PHD

Novel synthetic approaches to polyhydroxylated indolizidines

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University of Bath

NOVEL SYNTHETIC APPROACHES TO POLYHYDROXYLATED INDOLIZIDINES

Submitted by Melvyn Edward Giles
for the degree of Ph.D.
of the University of Bath
1991

M. Giles

To my parents,

for their ever-present

support

ACKNOWLEDGEMENTS

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Finally, I am grateful to the SERC and to SmithKline Beecham Pharmaceuticals for providing a CASE studentship.

SUMMARY

The work described in this thesis is introduced by an account of the biological importance of hydroxylated indolizidines and this is followed by a review of previous synthetic efforts in this area.

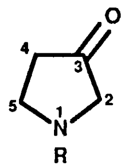
The generation and use of β-lithiated enol ethers as potential synthetic equivalents of a 3-pyrrolidinone enolate is described, and the synthesis of novel 2-alkylidene-3-pyrrolidinones and 2-alkyl-3-methoxypyrroles has been achieved.

An alternative approach utilizes the dianion derived from a β-keto ester as a general equivalent of the desired enolate, and this method represents the first successful solution to the problem of the non-selective enolization of 3-pyrrolidinones. A variety of 2-substituted-3-pyrrolidinones have been prepared using this methodology, including alkyl, dialkyl and aldol adducts.

The utility of the β-keto ester dianion for the assembly of polyhydroxylated indolizidines is exemplified by the synthesis of 8-epicastanospermine, in six steps and 22% overall yield, from an aldol precursor. The parallel synthesis of a novel tetrahydroxyindolizidine stereoisomer, in 11% overall yield from an aldol precursor, is also described.

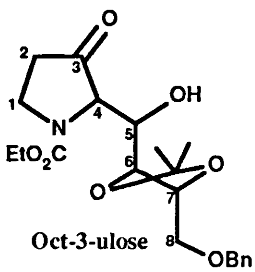
NOMENCLATURE

In general, the numbering system derived from the 3-pyrrolidinone series has been adopted for convenience, when referring to the pyrrolidine nucleus of the structures described in the Introduction, Section 3, and the Results and Discussion, Sections 1 and 2, of this thesis.

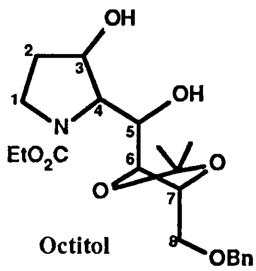


3-Pyrrolidinone

The numbering system derived from carbohydrate nomenclature has been used for the aldol adducts and derivatives described in the Results and Dicussion, Section 3, such as the oct-3-ulose and the octitol shown below.



Oct-3-ulose



Octitol

The indolizidine numbering system has been employed for derivatives containing the indolizidine core structure (see Introduction, page 1).

In the Experimental section, compounds have been numbered according to their names.

ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
c	concentrated
cat	catalytic
C.I.	chemical ionization
cf.	compare
*m*CPBA	*meta*-chloroperoxybenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)-pyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulphoxide
E^+	electrophile
E.I.	electron impact
eq	equivalents
FAB	fast atom bombardment
Glc	glucose
Glc*N*Ac	*N*-acetylglucosamine
h	hours
HIV	human immunodeficiency virus

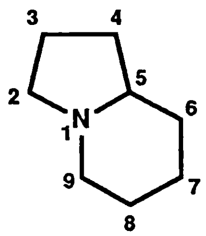
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
IR	infra red
J	coupling constant
Kcal	kilocalorie
LDA	lithium diisopropylamide
m	meta
M	molar
M^+	molecular ion
Man	mannose
Mes	2,4,6-trimethylbenzenesulphonyl
min	minutes
m.p.	melting point
Ms	methanesulphonyl
n	straight chain
NBS	*N*-bromosuccinimide
nmr	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
Nu	nucleophile
o	ortho
p	para
py	pyridine
ppm	parts per million
Pv	trimethylacetyl
R_f	retention factor
RT	room temperature
s	secondary
tert(*t*)	tertiary

TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulphonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl, 4-methylbenzenesulphonyl
Δ	heat
δ	chemical shift

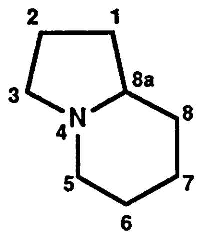
CONTENTS

RESULTS AND DISCUSSION

INTRODUCTION

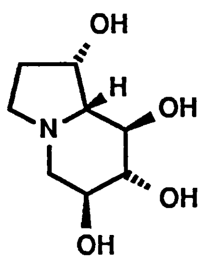


1-Azabicyclo[4.3.0]nonane

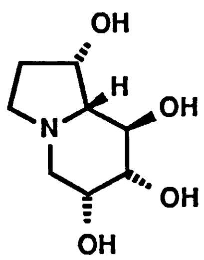


δ-Coniceine

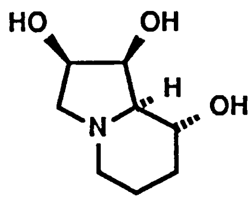
Fig. 1



Castanospermine

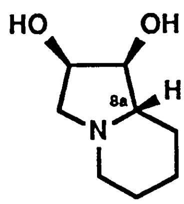


6-Epicastanospermine



Swainsonine

Fig. 2



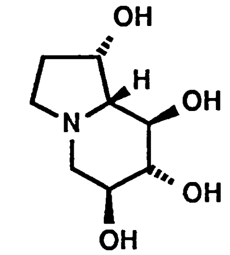
(1)

INTRODUCTION

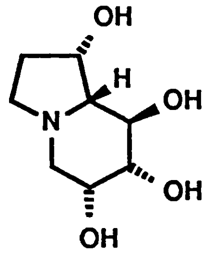
1 *Polyhydroxylated Indolizidine Alkaloids - Occurrence and Biological Activity*

1.1 Occurrence

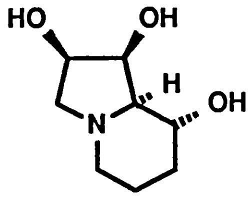
The indolizidine alkaloids[1] are a group of naturally-occurring compounds which incorporate the 1-azabicyclo[4.3.0]nonane nucleus as a characteristic structural feature. The synthetic product δ-coniceine,[1b] which is often mistakenly cited as a natural product,[2a] represents the structural prototype for this class of alkaloids (Fig. 1). Many substituted examples are known,[1b] but only three polyhydroxylated indolizidine alkaloids have been isolated from natural sources to date (Fig. 2). Castanospermine[2] occurs along with its 6-epi-isomer[16] in the Australian legume *Castanospermum australe*.[2a] Recently, a second plant source of castanospermine, *Alexa leiopetala*, was discovered.[2b] The structurally related alkaloid, swainsonine,[3] occurs in the plant *Swainsona canescens*,[3a] the spotted locoweed *Astragalus lentiginosus*,[3b] and the fungi *Rhizoctonia leguminicola*[3c] and *Metahizium anisopliae* F-3622.[3d] Very recently, a dihydroxyindolizidine **(1)** was isolated from *Rhizoctonia legumicola*[4] and there is evidence suggesting that **(1)** is an advanced intermediate along the biosynthetic pathway leading to swainsonine.[5] Clearly **(1)** must undergo epimerization at C-8a as well as oxidation of the piperidine ring in this fungus. These hydroxylated indolizidine alkaloids have aroused much interest because of their intriguing biological activities.



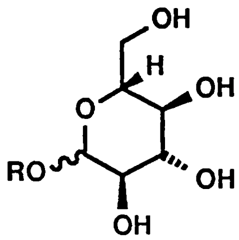
Castanospermine



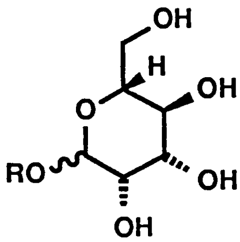
6-Epicastanospermine



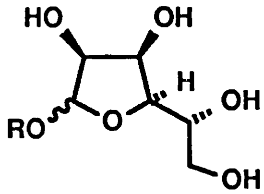
Swainsonine



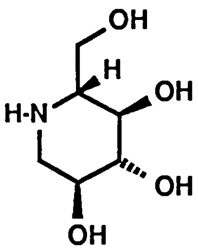
Glucopyranoside



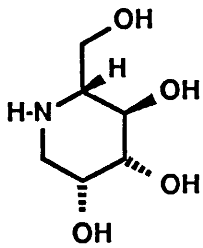
Mannopyranoside



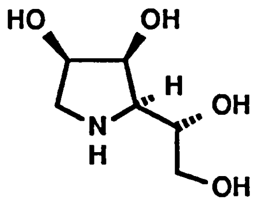
Mannofuranoside



Deoxynojirimycin



Deoxymannojirimycin



(2)

Scheme 1

1.2 Bioactive Indolizidines as Azasugar Analogues

Castanospermine, 6-epicastanospermine and swainsonine have all been found to inhibit certain glycosidases, the enzymes responsible for glycoside hydrolysis and/or glycosyl transfer in biological systems.[6,7] Structural relationships between each of these alkaloids and certain glycosides are apparent (Scheme 1). Thus, the piperidine ring of castanospermine is structurally related to the glucopyranosides whereas the corresponding unit of 6-epicastanospermine bears a stereochemical resemblance to the mannopyranosides. Swainsonine may be related to the mannofuranosides, through its pyrrolidine ring. Similar relationships can be seen for the hydroxylated piperidines, deoxynojirinicin[8] and deoxymannojirimicin[9] with glucopyranosides and mannopyranosides respectively. The synthetic pyrrolidine **(2)**[10] may also be regarded as a mannofuranoside analogue.

It is tempting to correlate structure with inhibitory activity by drawing analogies with sugars in which the heterocyclic oxygen atom is replaced by nitrogen. Thus, deoxynojirimicin, a glucopyranoside analogue, inhibits several glucosidases,[11] whereas deoxymannojirimicin, a mannopyranoside analogue, inhibits several mannosidases.[12] Similarly, castanospermine has been found to inhibit both α- and β-glucosidases[13] and swainsonine is an inhibitor of α-mannosidases.[14] In general, these inhibitory activities have been found to be competitive and reversible.

Several groups have invoked a biochemical model to explain the mechanism of glycosidase inhibition by this group by alkaloids, whereby the protonated form of the amine-based inhibitor acts as a mimic for the putative, enzyme-associated pyranosyl cation generated by acid-catalyzed cleavage of the exocyclic (anomeric) carbon-oxygen bond of the substrate.[3c,6,14,15] Thus, the

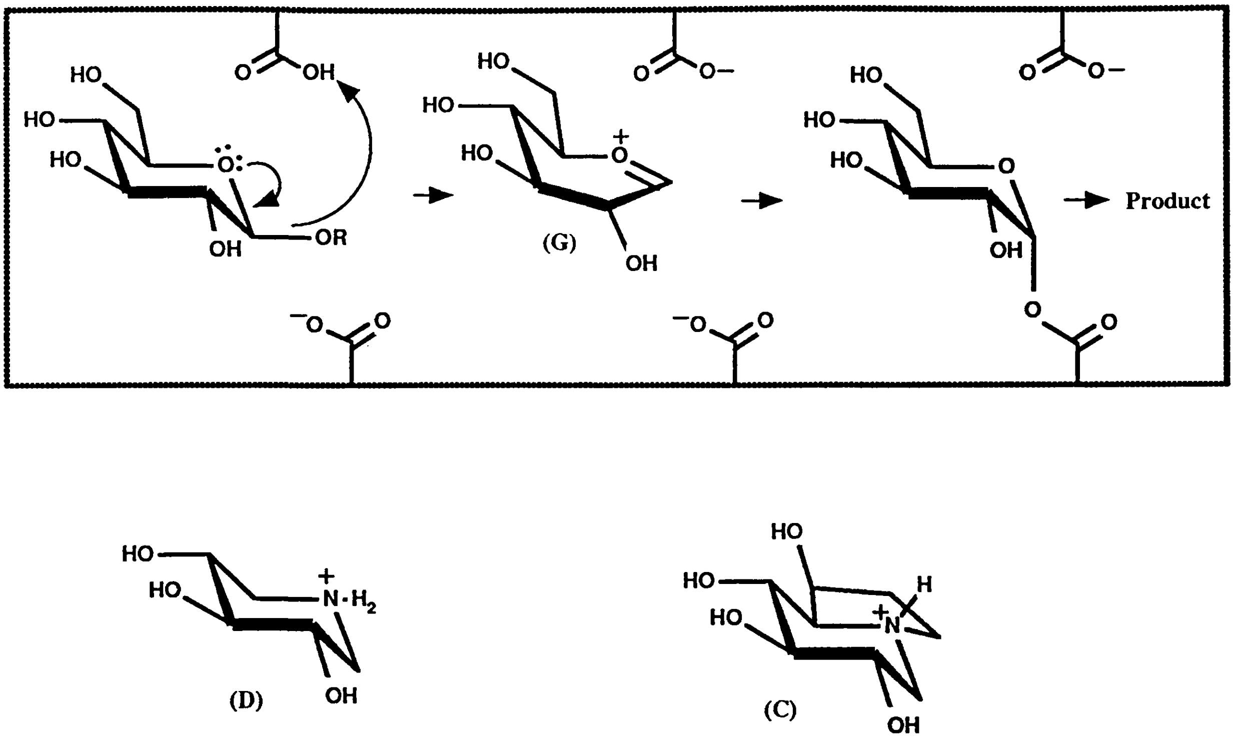


Fig. 3

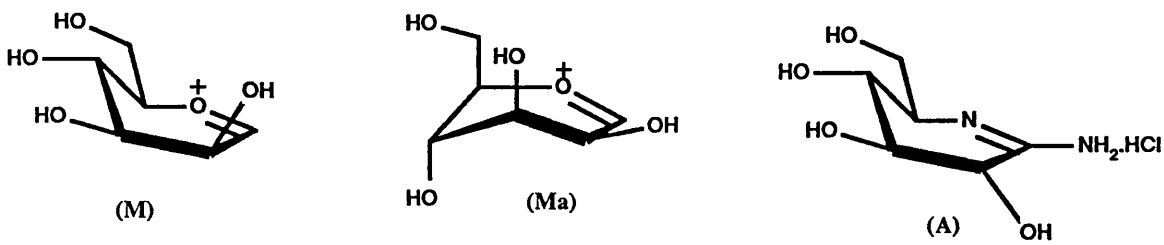
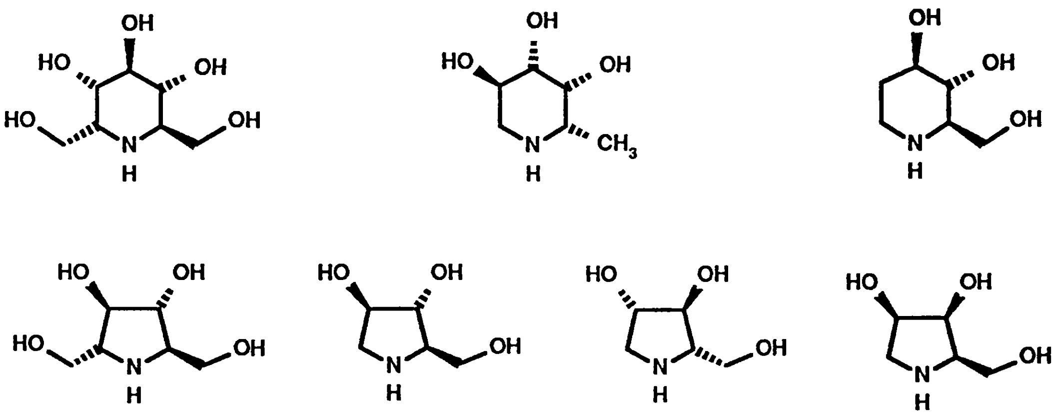


Fig. 4

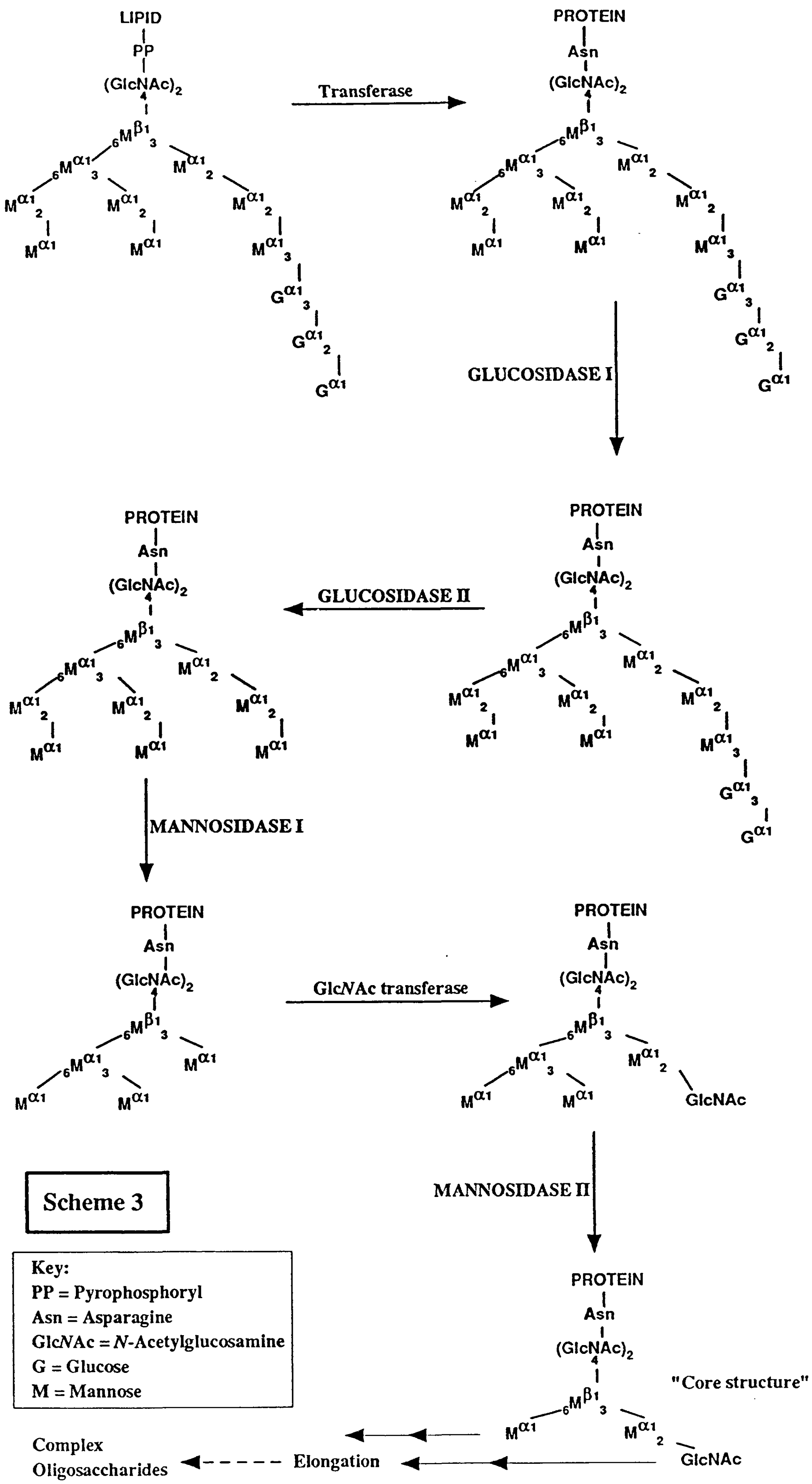


Scheme 2

protonated forms of deoxynojirimicin (**D**) and castanospermine (**C**) act as mimics for glucopyranosyl cation (**G**) (Fig. 3). Similarly, the observed activity of swainsonine has been attributed to its apparent similarity to the mannopyranosyl cation (**M**).

However, these simple structure-activity correlations do not always hold. For example, 6-epicastanospermine, an apparent mannopyranoside analogue, inhibits amyloglucosidase (an α-glucosidase) but <u>not</u> α- or β-mannosidases,[16] and castanospermine also inhibits β-xylosidase,[13b] β-glucocerebrosidase[13b] and sucrase.[17] Furthermore, it is not always easy to predict the activity of a number of other known natural and synthetic glycosidase inhibitors shown in Scheme 2.[18,19] Fleet has drawn attention to the stereochemical and electronic differences between the pyranosyl cation and the proposed amine-based mimic and this has led to an alternative explanation.[19] The powerful mannosidase inhibitory activity exhibited by swainsonine and pyrrolidine (**2**) suggests that the azafuranose analogue of mannose is important despite the fact that the substrates for these mannosidase enzymes are mannopyranosides.[19] The observed inactivity of 6-epicastanospermine towards mannosidases is in keeping with this idea, since this molecule lacks the azamannofuranose substructure.[67a]

Nevertheless, recent calculations suggest that the mannopyranosyl cation prefers a triaxial half-chair conformation (**Ma**) and that most potent mannosidase inhibitors share its binding topography[20] (Fig. 4). In addition, Ganem and coworkers have shown that the amidine hydrochloride (**A**), which combines the correct charge and conformational characteristics of glucopyranosyl cation (**G**), is a broad spectrum inhibitor of glycosidases[21] (Figs. 3 and 4).



Scheme 3

Key:
PP = Pyrophosphoryl
Asn = Asparagine
GlcNAc = N-Acetylglucosamine
G = Glucose
M = Mannose

In any event, it is clear that glycosidase inhibitory activity cannot be predicted simply by comparison of the structure and stereochemistry of a particular aza-analogue with the appropriate sugar, and subtle alterations in the stereochemistry of these alkaloids may produce significant changes in their glycosidase inhibition profiles.

The inhibition of glycosidase enzymes is probably responsible for the antiviral, anticancer and immunoregulatory activities associated with certain polyhydroxylated indolizidines. For example, castanospermine exhibits anti-retroviral activity against the human immunodeficiency virus (HIV)[26,27] and both castanospermine and swainsonine inhibit experimental metastasis in some cancer cell lines.[29] Swainsonine has also been shown to regulate the production of certain cells of the immune system.[31] It is likely that all these effects are a consequence of the glycosidase inhibitory activity associated with the alkaloids, and the resulting disruption of normal oligosaccharide processing in animal cells when these inhibitors are present. This aspect of their biological activity is discussed in more detail in Section 1.3, below.

1.3 Oligosaccharide Processing in the Biosynthesis of Glycoproteins

The pathway for the biosynthesis of the oligosaccharide portion of asparagine-linked glycoproteins is well characterized.[22,23a] A diagrammatic representation of this pathway is shown in Scheme 3. The initially formed, lipid-linked oligosaccharide is first transferred to the proteins and the newly-formed glycoprotein then undergoes a series of "trimming" reactions whereby sugar residues are removed sequentially by glycosidase enzymes. The outermost α-1,2-linked glucose is removed by an α-1,2-glucosidase enzyme, glucosidase I. The next two α-1,3-linked glucose residues are then removed by an α-1,3-glucosidase, glucosidase II. An α-1,2-mannosidase enzyme, mannosidase I can now remove all α-1,2-linked mannose residues, leaving the Man_5 $(GlcNAc)_2$-protein. This structure is a substrate for a Glc*N*Ac transferase, which adds a Glc*N*Ac unit to the mannose that is linked α-1,3 to the β-linked mannose.

This transfer is the signal for an α-1,3 and α-1,6-mannosidase enzyme, mannosidae II, to remove the outer two mannoses giving the $GlcNAcMan_3$ $(GlcNAc)_2$-protein structure. This sequence contains the core region of the complex *N*-linked oligosaccharides found in cells. The majority of such oligosaccharides in glycoprotein biosynthesis are assembled from this core structure, which is a substrate for a number of transferase enzymes. Both branches of the core can be elongated by the transfer of monosaccharides residues such as Glc*N*Ac, galactose, fucose and sialic acid, to give the complex glycosylated products characteristic of normal glycoprotein biosynthesis.

Because this biosynthetic pathway involves glycosidases, there is an opportunity for glycosidase inhibitors, such as castanospermine and swainsonine, to interfere with the overall process at several stages. When the effects of these two alkaloids on this and similar pathways were examined *in vitro*, castanospermine was found to be a potent glucosidase I inhibitor[(23)] and swainsonine an effective mannosidase II inhibitor.[(24)] Thus, in the presence of castanospermine, the trimming process is effectively blocked resulting in a build-up of high-mannose oligosaccharide structures of type $Glc_3Man_9(GlcNAc)_2$ - protein. However, in the presence of swainsonine, the pathway is affected at a much later stage and a preponderance of $GlcNAcMan_5(GlcNAc)_2$-protein may be produced. The right-hand branch of this structure bears a Glc*N*Ac residue and is recognised by transferase enzymes. Thus, hybrid oligosaccharide structures may be produced, where only one branch of the core has been elongated. Such interference with normal glycoprotein processing has profound implications because glycoproteins perform crucial functions in the biocycles of viruses and cancer cells. This has prompted the screening of alkaloids such as castanospermine and swainsonine for antiviral and anticancer activity and some of the results of these studies are discussed in Sections 1.4-1.6.

1.4 HIV and the Antiretroviral Activity of Castanospermine

The human immunodeficiency virus (HIV) expresses a glycoprotein, called gp120, on the surface of its protein coat. The process by which HIV infects the T-4 cells, lymphocytes pivotal in the operation of the immune system, involves viral recognition of a protein expressed on the surface of the T-4 cells.[(25)] This protein, called CD4, interacts with viral gp120 and although the nature of this interaction is not fully understood, it is apparently crucial for the initiation of an infectious cycle.[(26a)] Once bound to the T-4 cell, the virus will eventually enter thereby infecting the cell. The infected cells will, at some stage, express the original viral gp120 on their surfaces. When this happens, an infected cell can recognize, through gp120-CD4 interactions, a healthy, CD4-expressing cell. Fusion of the two cells, *via* syncytia formation can then occur. This process can take place repeatedly, resulting in the formation of large, multinucleated cells.[(26)] Such cell-cell fusion results in the spread of viral infection and ultimately leads to the death of the affected cells. Thus, the immune system becomes weakened due to a chronic depletion in T-4 cells and the infected organism is then vulnerable to opportunistic secondary infection.

The involvement of *N*-linked glycans in the gp120-CD4 interaction has been suggested because viral gp120 is known to be extremely heavily glycosylated.[(26a)] When HIV infected cells were incubated in the presence of castanospermine, syncytia formation between infected cells and

CD4-expressing cells was completely inhibited and viral infectivity was reduced.[26,27] At the concentrations employed the alkaloid exhibited low cell toxicity, although a subsequent *in vivo* study showed that castanospermine was toxic in mice.[27] Miedema and coworkers proposed that castanospermine prevents normal processing of the oligosaccharide portion of gp120, or its precursor, and the resulting carbohydrate perturbations lead to lower gp120-CD4 affinities.[26a] Oligosaccharide dysfunction is also apparently involved in the antiretroviral activity displayed by castanospermine against murine leukemia virus.[28]

1.5 Anticancer and Immunoregulatory Activity

The anticancer activity of castanospermine and swainsonine has also been attributed to the interference of these alkaloids in oligosaccharide biosynthesis.[29] Primary tumours spread to a number of secondary sites *in vivo* by a process known as metastasis involving a complex series of sequential biochemical interactions.[30] There is good evidence that oligosaccharides present on the surface of tumour cells play a significant role in metastasis.[29b] Castanospermine and swainsonine were both found to inhibit experimental metastasis of murine melanoma cells *in vivo* at concentrations that did not produce any cytotoxic effects.[29] In addition, swainsonine augments the activation of killer cells in the immune system against certain types of tumour cell, and also facilitates the proliferation of other cells associated with the immune system.[31] These observations have been explained in terms of the effects of glycoprotein-processing modulators on immunoregulatory glycopeptides.

1.6 Other Aspects of Biological Activity

Recently, castanospermine has been shown to reduce the density and responsiveness of nicotinic acetylcholine receptors expressed in mammalian cells.[32] The mechanism by which these effects are manifested is unknown, though it seems likely that the carbohydrate moiety of the acetylcholine receptor may well affect its functional properties. Castanospermine also shows promise as a lead for new antidiabetic agents.[33]

Thus far, the third polyhydroxylated indolizidine, 6-epicastanospermine, has not been widely screened for biological activity. Both castanospermine and 6-epicastanospermine have been shown to possess aphid antifeedant activity,[34] and one recent study confirmed castanospermine as an antiviral agent whereas 6-epicastanospermine was found to be inactive.[35]

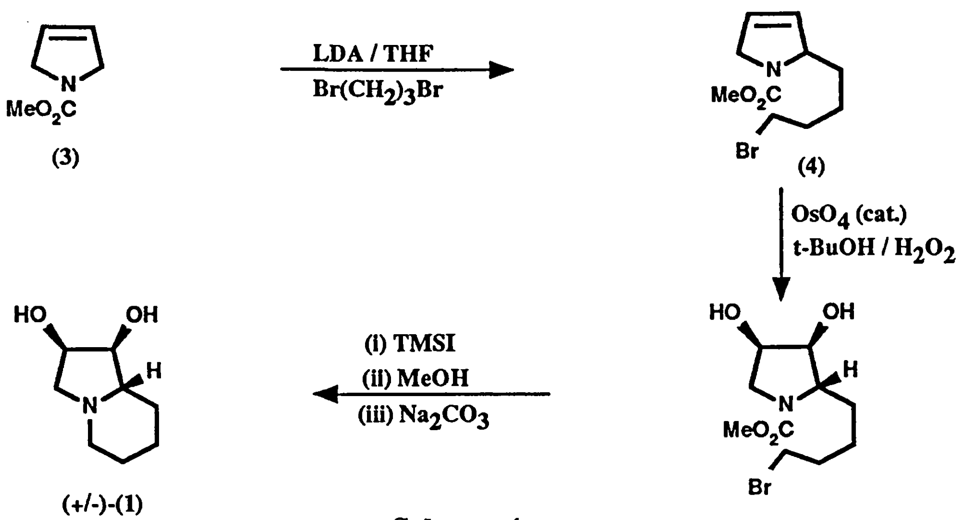
Finally, recent reports suggest that certain derivatives of castanospermine and related compounds, notably alkylated and acylated variants, may find uses as antiretroviral agents because of their dramatically increased potencies.[36]

1.7 The Need for Novel Azasugar Analogues

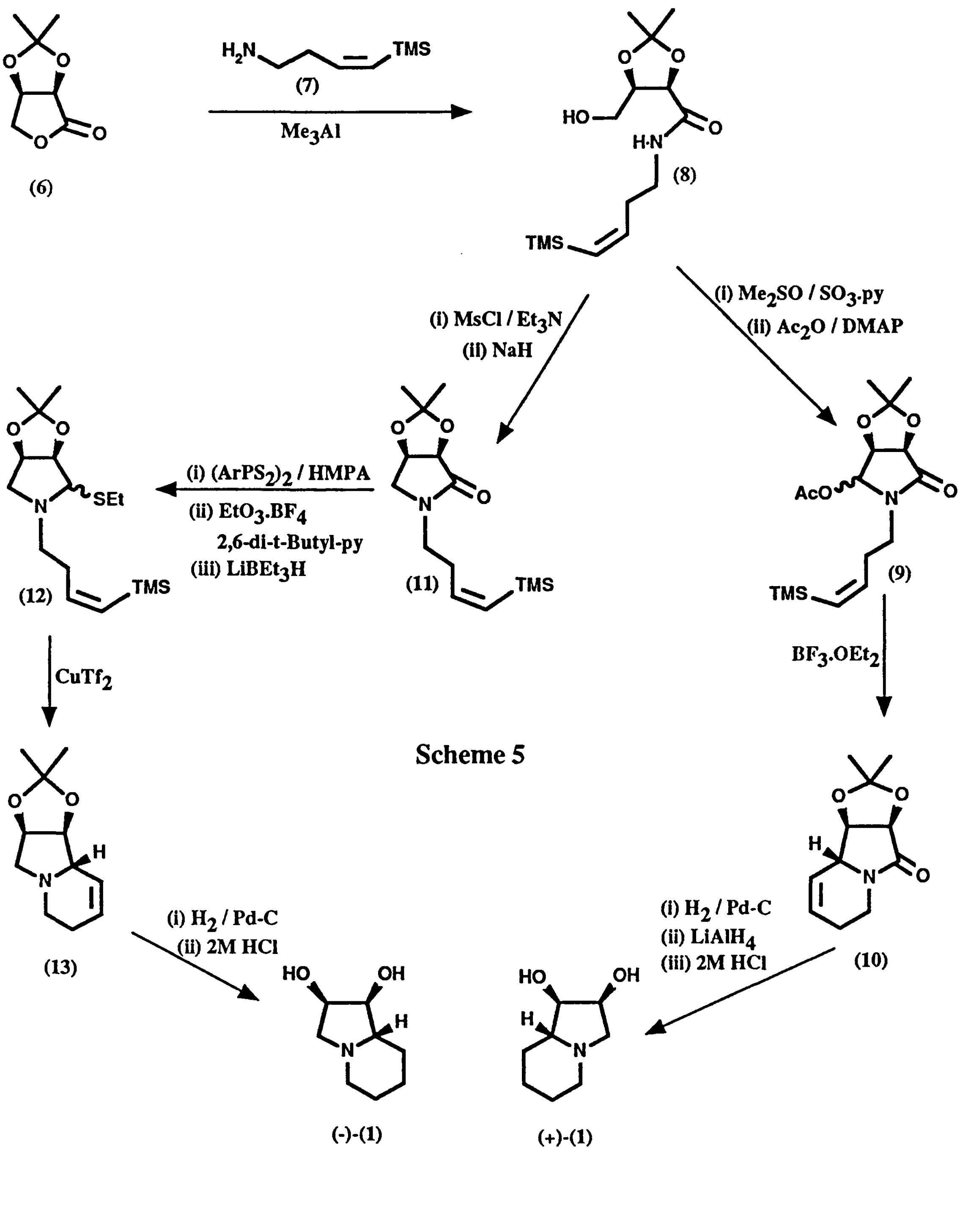
The lack of a well-defined structure-activity model for glycosidase inhibition by known azasugar analogues precludes predictions of activity based on the known degree and substitution pattern of hydroxylation and the stereochemistry at hydroxyl-bearing centres. Screening of compounds which possess novel features in these respects may provide clues to the mechanism of action of hydroxylated indolizidines as glycosidase inhibitors.

Furthermore, the bioactive characteristics of such compounds may vary with respect to: (i) the selectivity of enzyme inhibition and (ii) the stage at which glycosidase inhibition occurs in the oligosaccharide trimming sequence.

Consideration of both of these aspects is important in the search for new and effectie chemotherapeutic agents based on these types of molecules. The potential rewards for the successful development of such agents are manifold. It is not surprising, then, that the synthesis of azasugar analogues is an area of great current interest to organic chemists. The synthetic effort already invested in this area over recent years, has resulted in the publication of a number of approaches to a variety of hydroxylated indolizidine alkaloids. A review of the major synthetic achievements in this area is presented in Section 2, below.



Scheme 4



Scheme 5

2 *The Synthesis of Hydroxylated Indolizidines*

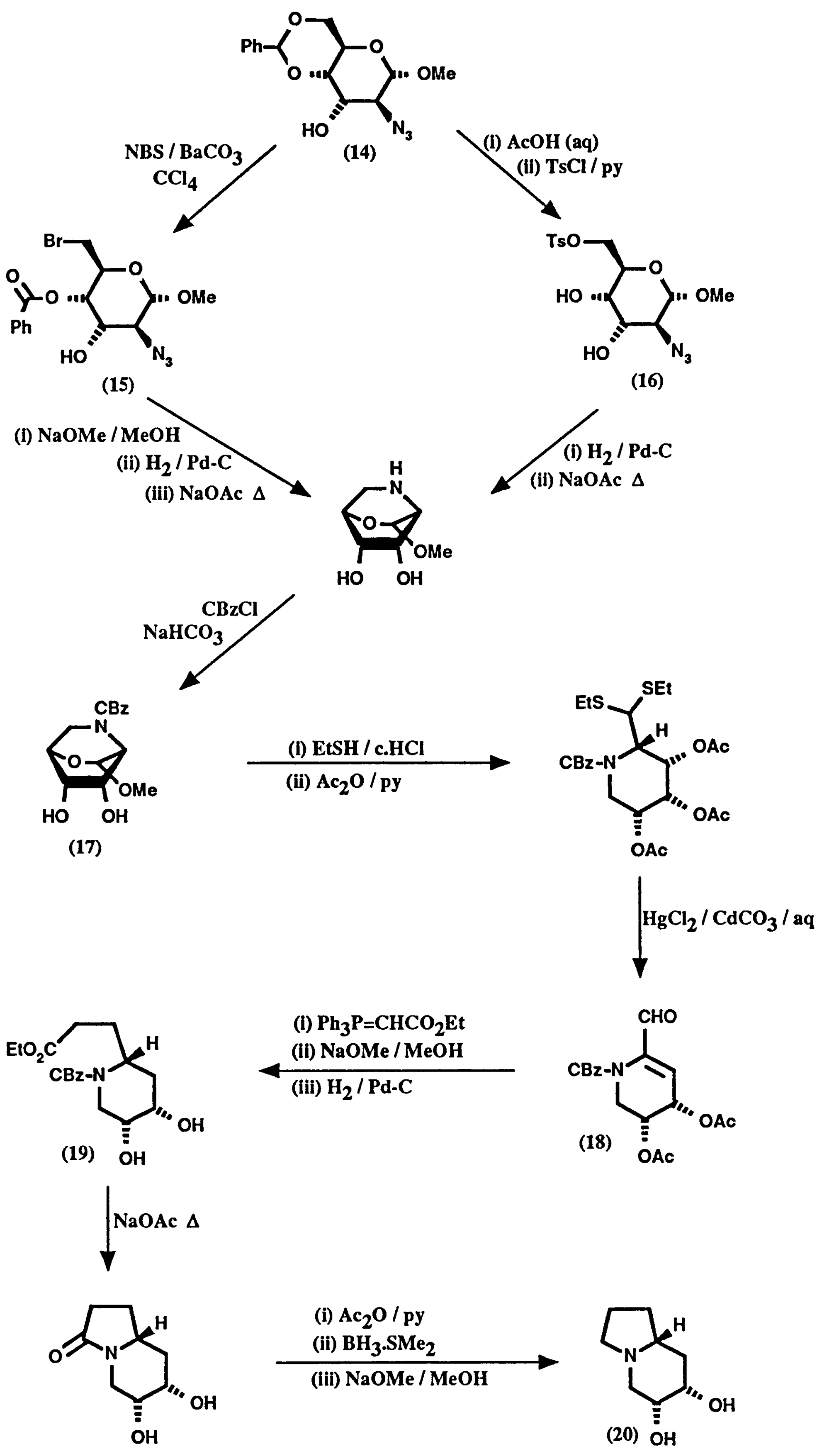
2.1 *The Synthesis of Dihydroxyindolizidines*

With the bulk of the chemical and biological interest centred around the trihydroxy- and tetrahydroxyindolizidines, the synthesis of dihydroxy-derivatives has received limited attention.

The racemic *cis*-dihydroxyindolizidine **(1)** was prepared by Colegate *et al* in 1984[37], before one enantiomer was identified as a natural product.[4] Allylation of the anion generated from 3-pyrroline **(3)** by deprotonation with LDA, gave the racemic α-alkylated compound **(4)** (Scheme 4). Dihydroxylation of **(4)**, followed by *N*-deprotection and cyclization afforded (±)-**(1)**.

The racemate was tested for biological activity and was found to exhibit only weak inhibition of α-mannosidase and α-glucosidase enzymes.

In a subsequent study, Overman and Heitz synthesized each enantiomer of **(1)** using enantiodivergent technology[38] (Scheme 5). Lactone acetonide **(6)**, available in enantiomerically pure form from D-isoascorbic acid, was subjected to aminolysis with amine **(7)** and trimethylaluminium to give amide **(8)**. This intermediate could be converted to either enantiomer of **(1)** *via* iminium ion/vinylsilane cyclization methodology. Oxidation of **(8)** followed by acetylation of the intermediate hydroxy lactam afforded **(9)** as a mixture of diastereoisomers. Cyclization of an *N*-acyliminium ion intermediate derived from **(9)** by treatment with a Lewis acid gave **(10)**, which was converted to (+)-**(1)** by reduction followed by hydrolysis. The synthesis of (-)-**(1)** from **(8)** involved a similar cyclization reaction. The α-thio amine **(12)** was prepared in

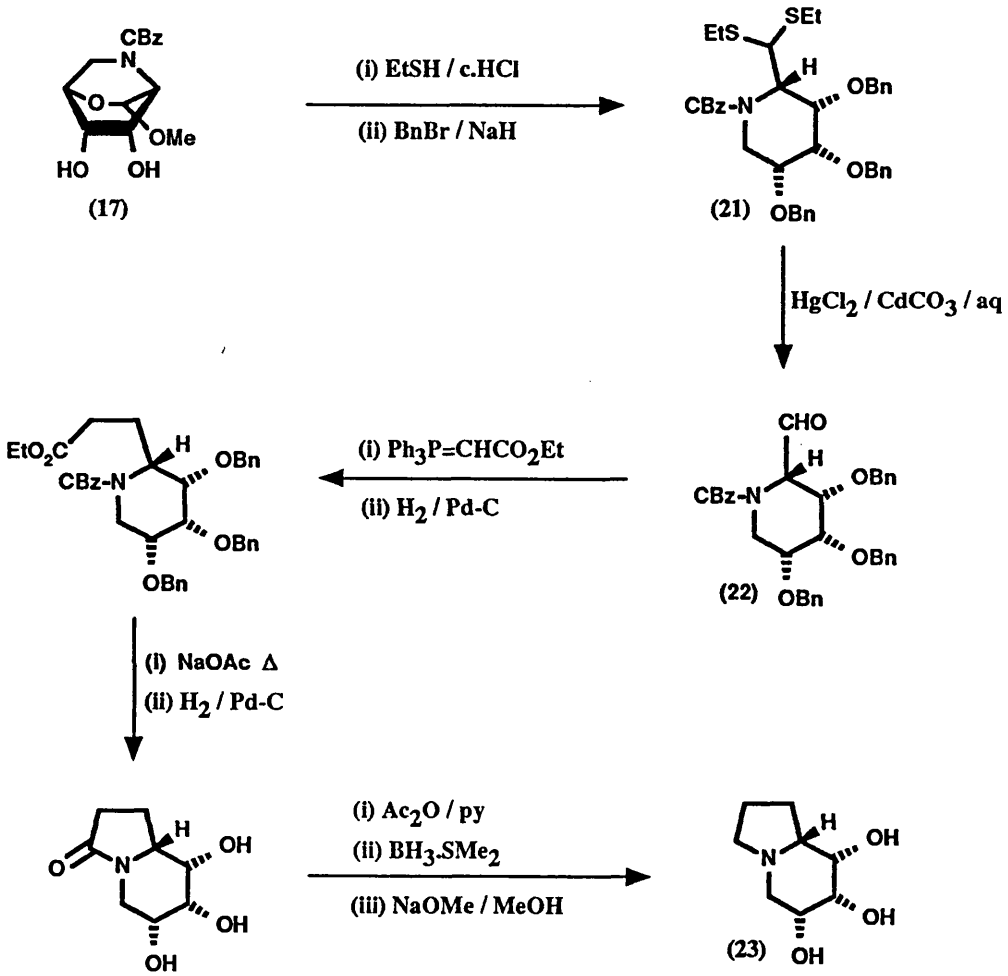


Scheme 6

three steps from lactam **(11)**, the dehydration product of **(8)**. In this case, the electrophilic centre of the iminium ion generated from **(12)** was situated on the other side of the nitrogen atom, and cyclization to give **(13)** ensued, which was converted to (-)-**(1)**.

This synthesis confirmed the absolute stereochemistry of the natural product as 1S,2R,8aS.[5] Both enantiomers of **(1)** were synthesized in overall yields of approximately 20%.

Richardson and coworkers have reported the enantiospecific synthesis of another dihydroxyindolizidine, which was prepared *en route* to a trihydroxy derivative (see Section 2.2.1.1).[39] The starting material was the azido sugar derivative **(14)** available in four steps from methyl-α-D-glucopyranoside (Scheme 6). Conversion of **(14)** to the bicyclic carbamate **(17)** was achieved in one of two ways. Oxidative cleavage of the benzylidene moiety of **(14)** using *N*-bromosuccinimide gave the bromobenzoate **(15)**.[40] De-*O*-benzoylation was followed by reduction of the azido group to the amine which underwent intramolecular *N*-alkylation, *via* a boat conformer, providing **(17)** after protection of the intermediate bicyclic amine. An alternative procedure involved hydrolysis of **(14)** and tosylation of the resulting primary hydroxyl function to afford **(16)**, which also contained the requisite methylene-borne leaving group required for subsequent intramolecular displacement. The preparation of key intermediate **(17)** represents the synthesis of a six-membered nitrogen heterocycle in enantiospecific fashion, from a sugar-derived precursor **(4)**. Subsequent assembly of the indolizidine system was accomplished *via* a two-carbon homologation of the unsaturated aldehyde **(18)**, prepared from **(17)** by a series of transformations involving thioacetalization, *O*-acetylation and dethioacetalization. The major isomer **(19)**, obtained by catalytic hydrogenation, was converted to the


CBz
OMe
HO OH
(17)
(i) EtSH / c.HCl
(ii) BnBr / NaH
SEt
EtS
H
OBn
CBz-N
OBn
(21) OBn
HgCl2 / CdCO3 / aq
CHO
H
OBn
CBz-N
OBn
(22) OBn
(i) Ph3P=CHCO2Et
(ii) H2 / Pd-C
EtO2C
H
OBn
CBz-N
OBn
OBn
(i) NaOAc Δ
(ii) H2 / Pd-C
H
OH
O
N
OH
OH
(i) Ac2O / py
(ii) BH3.SMe2
(iii) NaOMe / MeOH
H
OH
N
OH
(23) OH

Scheme 7

dihydroxyindolizidine **(20)** using standard techniques. No yield was quoted for the mercuric chloride mediated dethioacetalization reaction in which elimination of the 3-acetoxy group occurred.

6,7-Dihydroxyindolizidine **(20)** did not exhibit any significant inhibitory activity against a range of glycosidase enzymes.[39b]

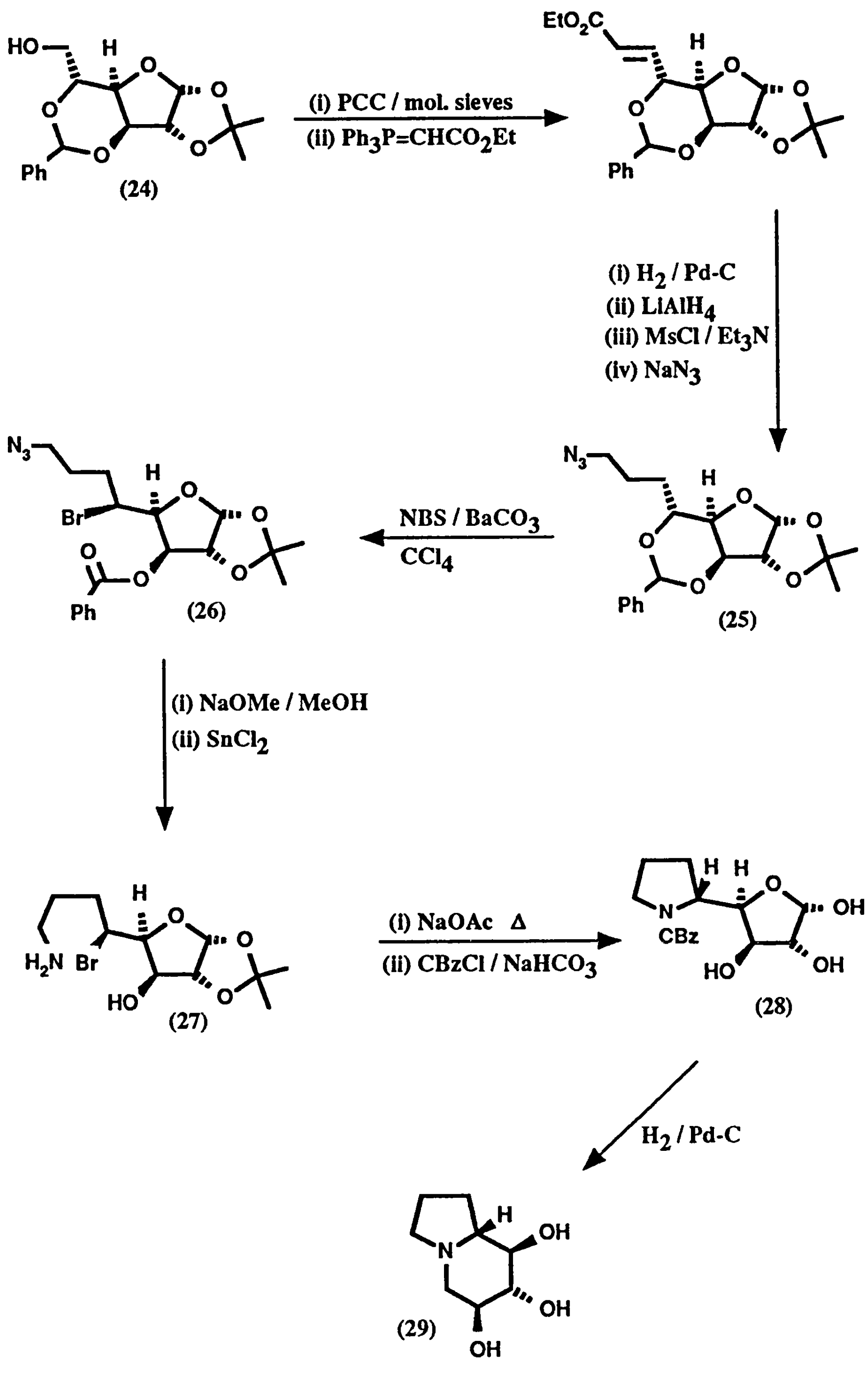
2.2 The Synthesis of Trihydroxyindolizidines

2.2.1 Deoxy-castanospermines

2.2.1.1 Synthesis from Carbohydrate Precursors

Bicyclic intermediate **(17)**, used in the synthesis of dihydroxyindolizidine **(20)**, was also employed by Richardson in the preparation of a deoxy-castanospermine derivative.[39] Elimination of the *O*-substituted-3-hydroxyl group could be avoided if a different mode of protection was adopted. Thus, thioacetalization of **(17)** followed by *O*-benzylation gave **(21)**, which underwent smooth hydrolysis to give the tribenzyloxy-substituted aldehyde **(22)** (Scheme 7). Similar transformations to those used in the synthesis of **(20)** were applied to **(22)** to give (+)-1-deoxy-6,8-diepicastanospermine **(23)** in 25% yield from **(17)** (5.6% yield from **(14)**).

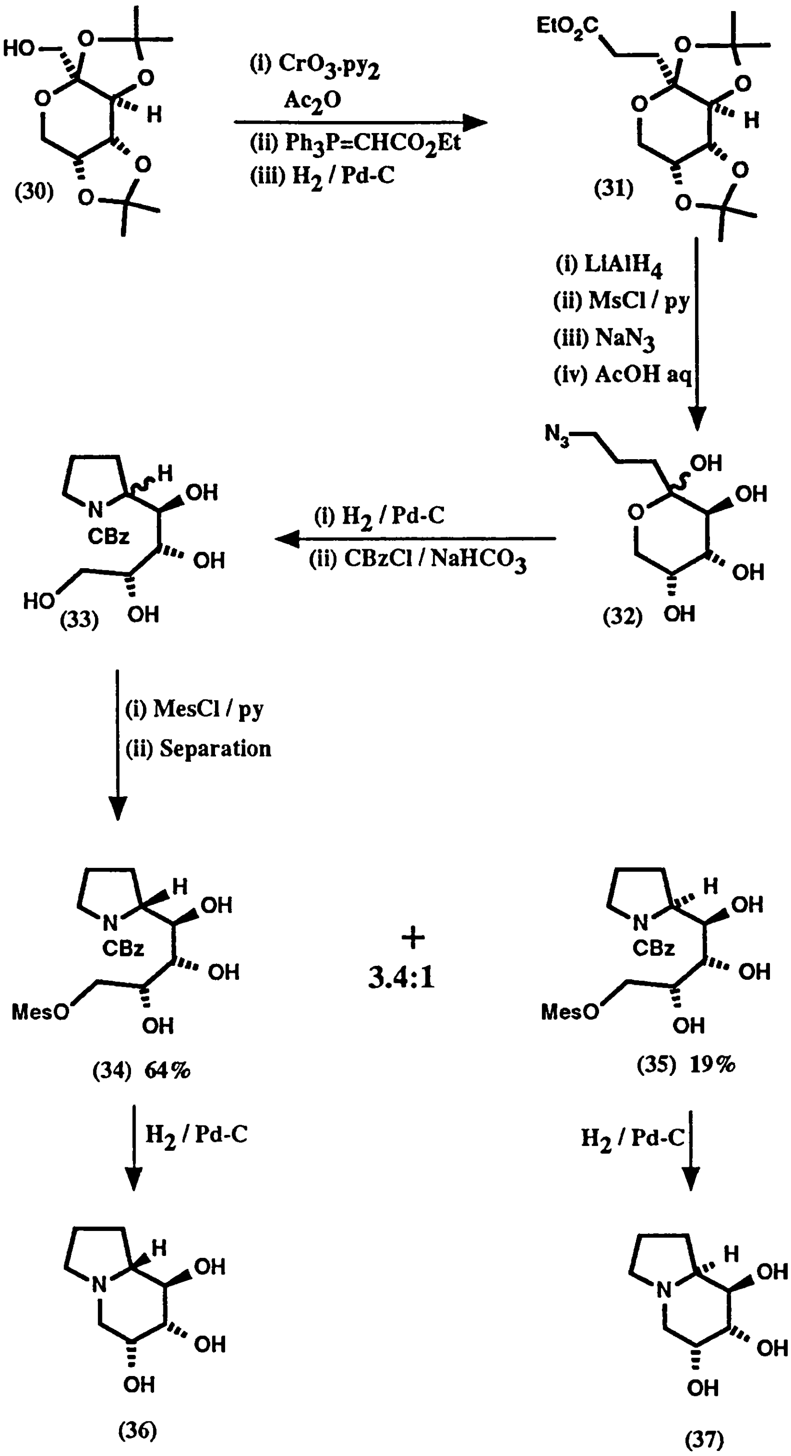
This compound displayed only weak glycosidase inhibitory activity.[39b]


(i) PCC / mol. sieves
(ii) Ph3P=CHCO2Et
(24)
(i) H2 / Pd-C
(ii) LiAlH4
(iii) MsCl / Et3N
(iv) NaN3
(25)
NBS / BaCO3
CCl4
(26)
(i) NaOMe / MeOH
(ii) SnCl2
(27)
(i) NaOAc Δ
(ii) CBzCl / NaHCO3
(28)
H2 / Pd-C
(29)

Scheme 8

Richardson *et al* have also published an enantiospecific synthesis of 1-deoxycastanospermine from an α-D-glucofuranoside derivative.[41] The known alcohol **(24)** was converted to azide **(25)** as shown in Scheme 8. Oxidative bromination of the benzylidene acetal in **(25)** with *N*-bromosuccinimide was a key step. This reaction, which was encountered previously *en route* to **(17)**, gave rise to the δ-azido bromide **(26)**. The 2-substituted-*N*-protected pyrrolidine **(28)** was prepared in five steps from **(26)**, *via* δ-amino bromide **(27)**. The synthesis was completed by hydrogenation of **(28)** which produced (+)-1-deoxycastanospermine **(29)** *via* intramolecular reductive amination, in an overall yield of 9.3% from **(24)**.

Trihydroxyindolizidine **(29)** was found to be a much weaker glycosidase inhibitor than castanospermine, indicating that the 1-hydroxyl group of the parent compound is important for inhibitory activity.[41b]

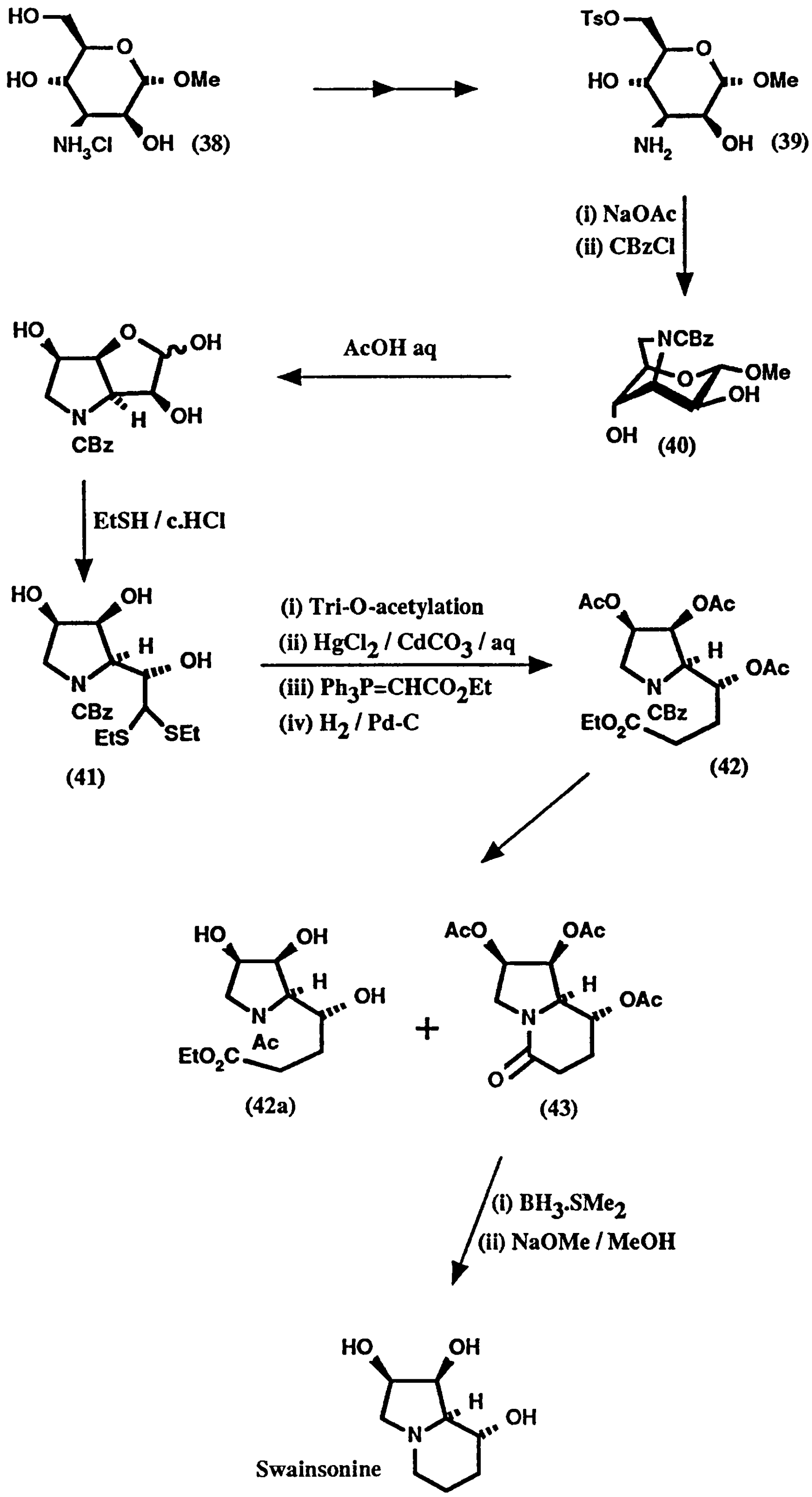


Scheme 9

Most recently, the same group reported the synthesis of two stereoisomers of 1-deoxycastanospermine.[42] Here, 6-epi-isomers were targeted by choosing a starting material of appropriate absolute stereochemistry. The β-D-fructopyranoside derivative **(30)**, readily available from D-fructose, was converted to the ester **(31)** which was transformed into azide **(32)** by routine chemical manipulation (Scheme 9). Construction of the pyrrolidine ring from **(32)** involved reductive amination of the derived amino hexose and this was effected by hydrogenation to give, after protection of the nitrogen centre, pyrrolidine **(33)** as a epimeric mixture at C-2. Chromatographic separation of the primary *O*-mesitylenesulphonates obtained from **(33)** afforded **(34)** and **(35)**. The major isomer was converted to (-)-1-deoxy-6-epicastanospermine **(36)** after *N*-deprotection and cyclization. Similar treatment of the minor isomer furnished (+)-1-deoxy-6,8a-diepicastanospermine **(37)**. The overall yields of **(36)** and **(37)** from **(31)** were 24 and 7% respectively.

Both isomers were found to inhibit the action of α-L-fucosidase but not α-D-mannosidase.[42]

A novel deoxycastanospermine derivative **(62)** has been obtained from a by-product of the penultimate reaction in a synthesis of swainsonine.[47] The formation of **(62)** is discussed in Section 2.2.2.1 (See Schemes 15 and 16). 6-deoxycastanospermine has been prepared by Sih *et al* from an intermediate that also provided access to castanospermine and 6,7-diepicastanospermine[73] (see Scheme 38).



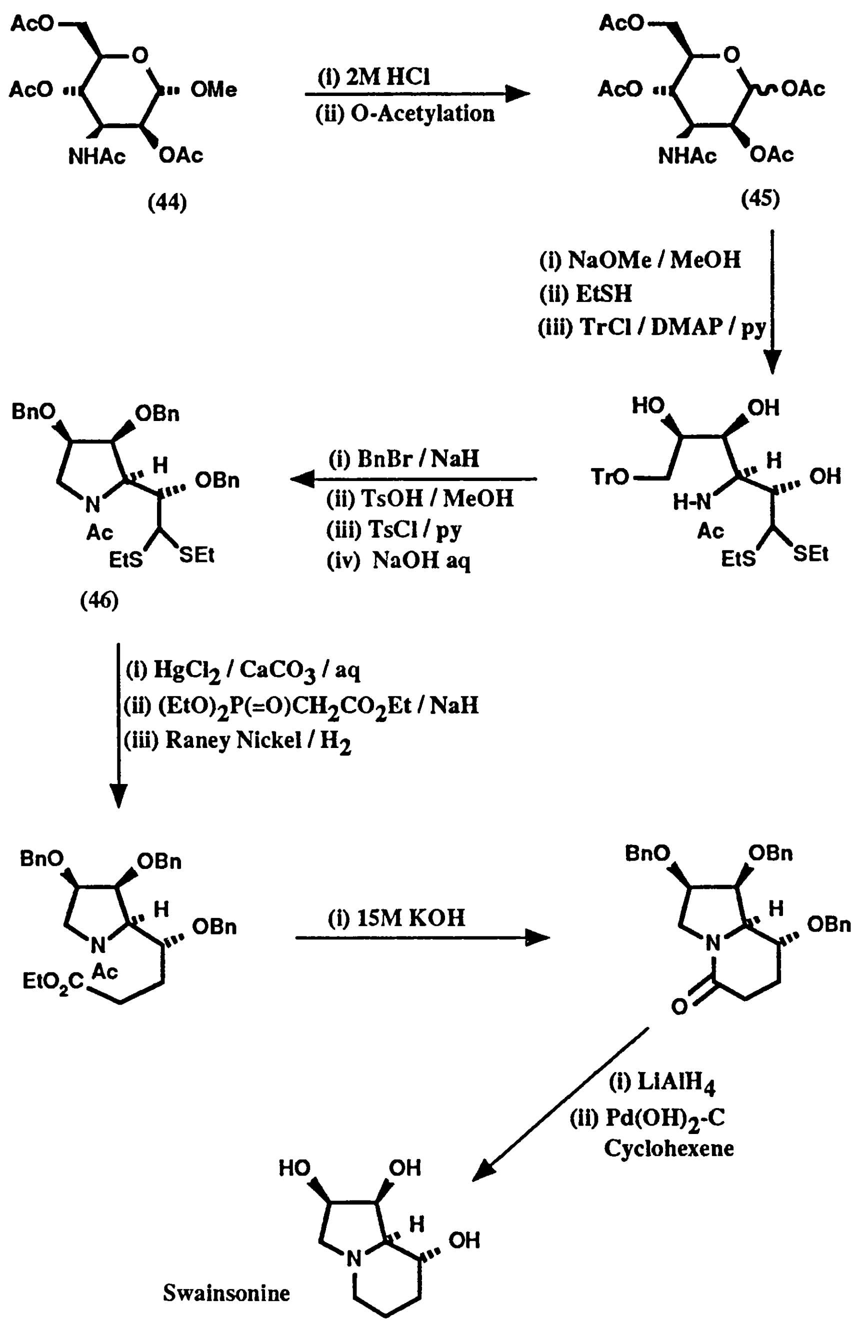
HO
O
HO
OMe
NH3Cl
OH
(38)
TsO
O
HO
OMe
NH2
OH
(39)
(i) NaOAc
(ii) CBzCl
NCBz
O
OMe
OH
OH
(40)
AcOH aq
HO
O
OH
N
H
OH
CBz
EtSH / c.HCl
HO
OH
H
OH
N
CBz
EtS
SEt
(41)
(i) Tri-O-acetylation
(ii) HgCl2 / CdCO3 / aq
(iii) Ph3P=CHCO2Et
(iv) H2 / Pd-C
AcO
OAc
H
OAc
N
EtO2C
CBz
(42)
HO
OH
H
OH
N
Ac
EtO2C
(42a)
+
AcO
OAc
H
OAc
N
O
(43)
(i) BH3.SMe2
(ii) NaOMe / MeOH
HO
OH
H
OH
N
Swainsonine

Scheme 10

2.2.2 Swainsonine and Stereoisomers

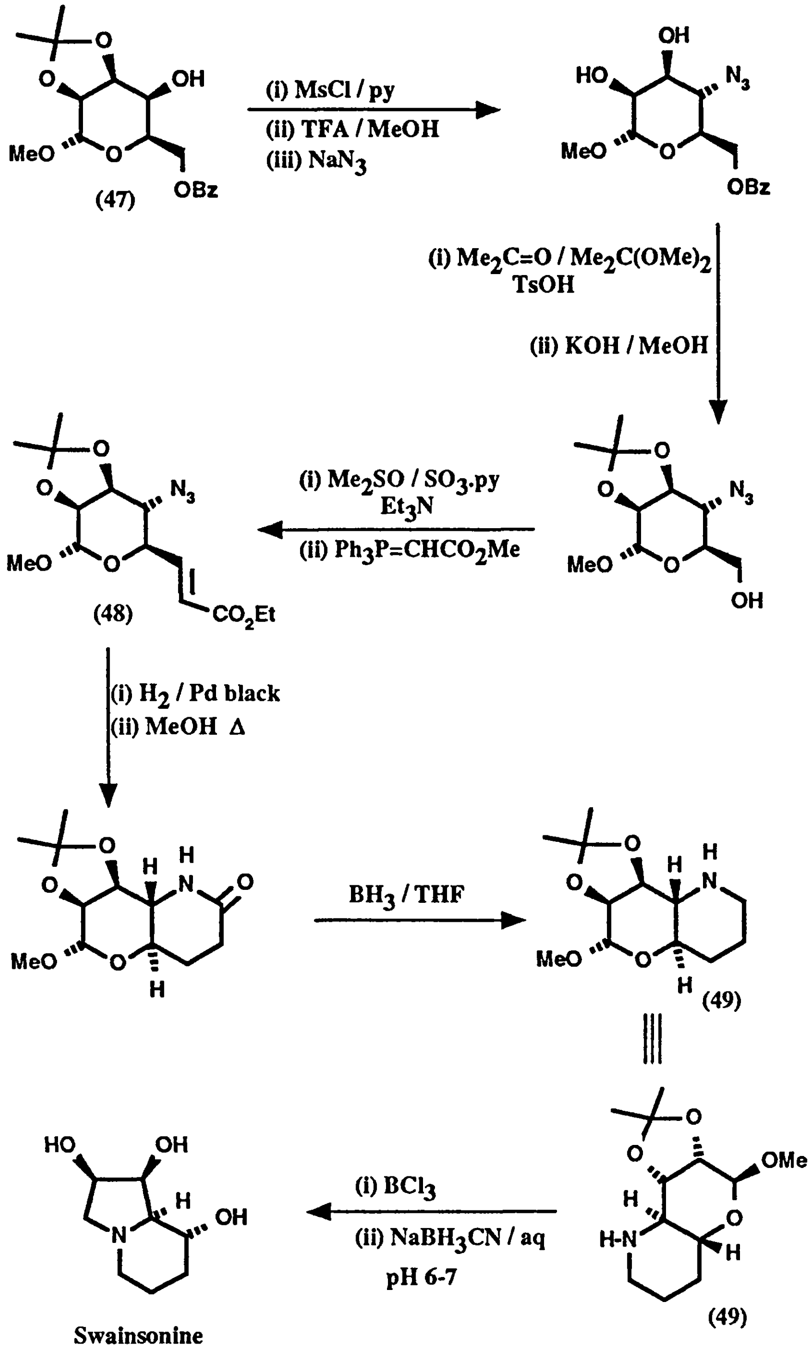
2.2.2.1 Synthesis from Carbohydrate Precursors

One of the first reported syntheses of swainsonine was accomplished by the Richardson group.[43] The starting material was methyl α-D-glucopyranoside which was used previously for the preparation of the versatile intermediate **(17)** (see Scheme 6). This starting material was converted to the mannopyranoside derivative **(38)** by a known procedure (Scheme 10). Cyclization of the amino toyslate derived from **(38)** followed by *N*-protection gave the bicyclic carbonate **(40)**, which contains the dioxygenated pyrrolidine ring required for elaboration to the natural product. On acid hydrolysis, **(40)** was converted to a bicyclic furanose which was treated with ethanethiol in the presence of hydrochloric acid to give dithioacetal **(41)**. Clearly **(41)** requires the introduction of a two carbon unit to complete the framework required for the indolizidine skeleton, and this was accomplished using a Wittig reaction on the derived aldehyde. Protection of all three hydroxyl groups was found to be necessary prior to olefination. Intramolecular *O*- to *N*-acetyl migration competed with cyclization of the intermediate amino ester (42), and equimolar quantities of hydroxy ester **(42a)** and lactam **(43)** were produced. Routine transformations converted **(43)** to (-)-swainsonine, which was obtained in 2.7% overall yield from **(38)**.


AcO
O
AcO
OMe
NHAc
OAc
(44)
(i) 2M HCl
(ii) O-Acetylation
AcO
O
AcO
OAc
NHAc
OAc
(45)
(i) NaOMe / MeOH
(ii) EtSH
(iii) TrCl / DMAP / py
HO
OH
TrO
H
OH
H-N
Ac
EtS
SEt
(i) BnBr / NaH
(ii) TsOH / MeOH
(iii) TsCl / py
(iv) NaOH aq
BnO
OBn
H
OBn
N
Ac
EtS
SEt
(46)
(i) HgCl2 / CaCO3 / aq
(ii) (EtO)2P(=O)CH2CO2Et / NaH
(iii) Raney Nickel / H2
BnO
OBn
H
OBn
N
EtO2C
Ac
(i) 15M KOH
BnO
OBn
H
OBn
N
O
(i) LiAlH4
(ii) Pd(OH)2-C
Cyclohexene
HO
OH
H
OH
N
Swainsonine

Scheme 11

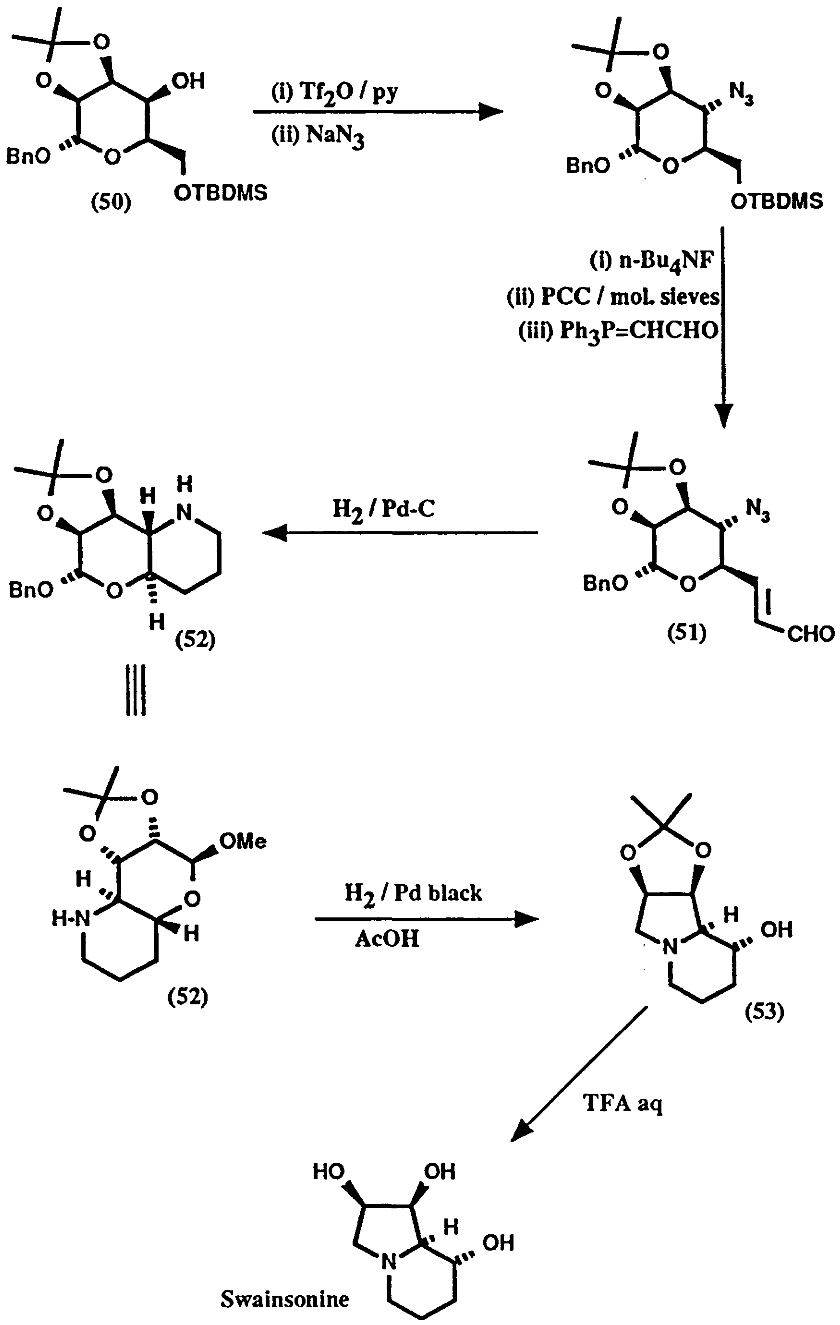
A similar approach was reported subsequently by Tadano *et al*[44] (Scheme 11), except that dithioacetalization of pyranose **(45)** was effected prior to pyrrolidine ring formation. The conversion of **(46)** to (-)-swainsonine was analogous to the elaboration of **(41)** in the previous synthesis and the authors quote an overall yield of 4% for this synthesis starting from **(44)**, which itself is readily available from a glucopyranoside derivative.



OH
HO
N_3
MeO
O
OBz
(i) MsCl / py
(ii) TFA / MeOH
(iii) NaN_3
(47)
(i) $Me_2C{=}O$ / $Me_2C(OMe)_2$
TsOH
(ii) KOH / MeOH
(i) Me_2SO / SO_3.py
Et_3N
(ii) $Ph_3P{=}CHCO_2Me$
(48)
CO_2Et
(i) H_2 / Pd black
(ii) MeOH Δ
BH_3 / THF
(49)
(i) BCl_3
(ii) $NaBH_3CN$ / aq
pH 6-7
OMe
H-N
Swainsonine

Scheme 12

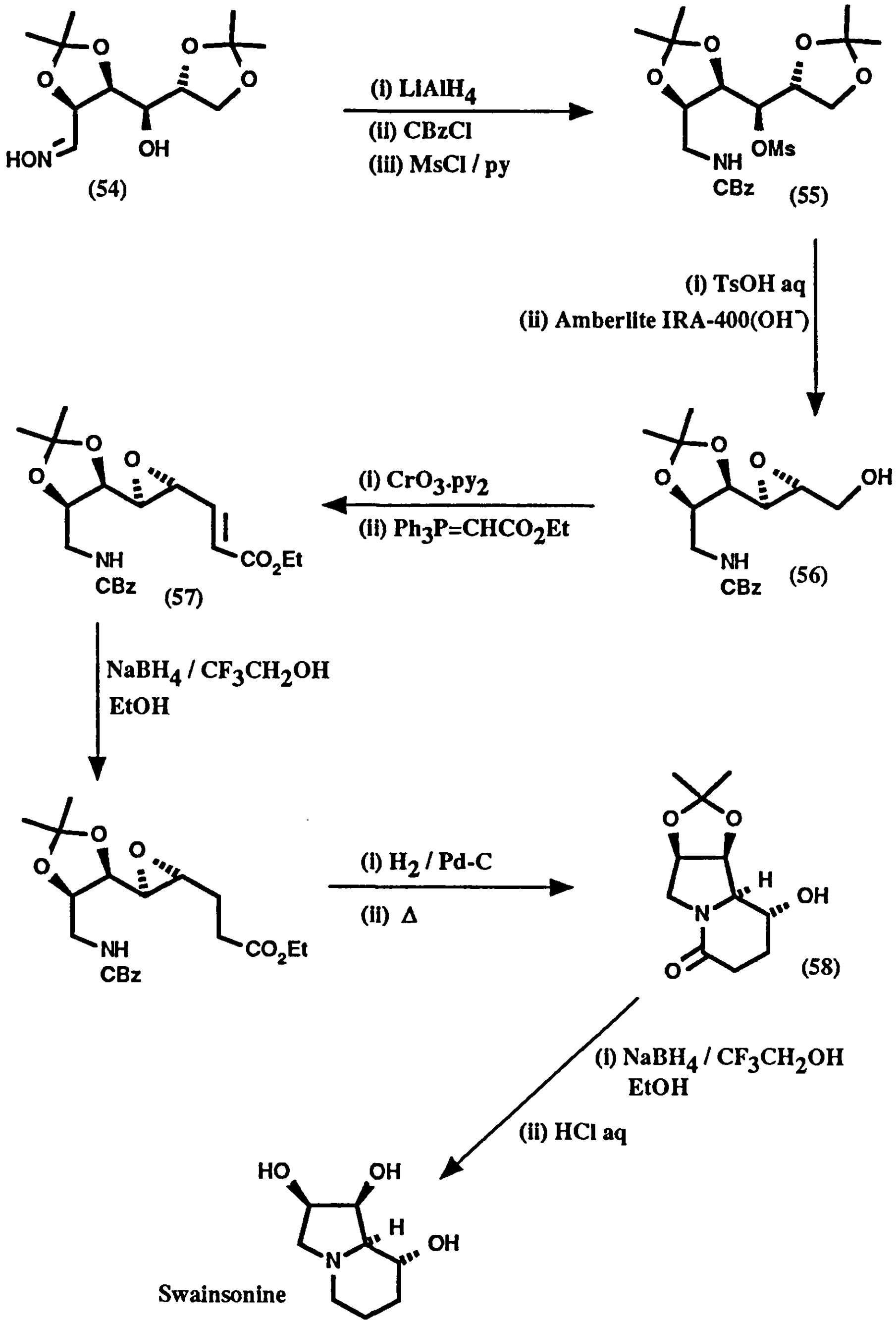
A different strategy was employed by Takaya and coworkers group.[45] The piperidine ring of swainsonine was formed first in this synthesis, which employed the talopyranoside **(47)**, available from D-mannose, as starting material (Scheme 12). Cyclization of the amino ester produced upon reduction of azide **(48)**, obtained in seven steps from **(47)**, gave a tricyclic lactam which was reduced to amine **(49)**. Demethylation of **(49)** could only be achieved using boron trichloride and subsequent reduction of the resulting intermediate, afforded (-)-swainsonine. The yield reported for this final conversion of **(49)** to swainsonine was only 1.8%, which makes this route somewhat impractical.


(i) Tf_2O / py
(ii) NaN_3
(50)
OTBDMS
BnO
OH
N_3
(i) n-Bu_4NF
(ii) PCC / mol. sieves
(iii) Ph_3P=CHCHO
H_2 / Pd-C
(51)
CHO
(52)
H_2 / Pd black
AcOH
OMe
H-N
(53)
OH
TFA aq
HO
Swainsonine

Scheme 13

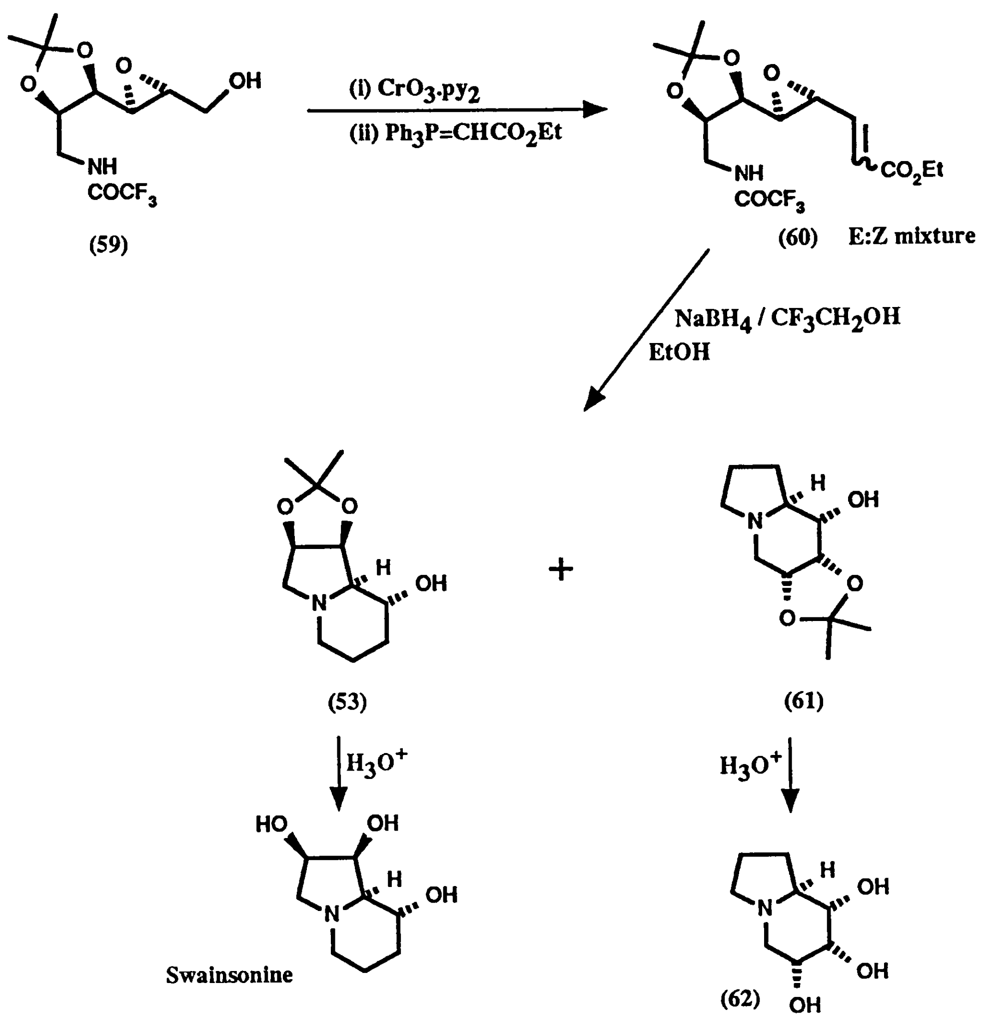
A very similar approach was later described by Fleet *et al*, in which some minor modifications led to a much more efficient synthesis.[46] Talopyranoside **(50)**, prepared in five steps and 71% yield from D-mannose, was converted to azido enal **(51)** (Scheme 13). This was accomplished using a similar series of reactions to those employed by Takaya for the synthesis of **(48)**. In this case, however, the final Wittig olefination reaction introduced an unsaturated aldehyde moiety instead of an unsaturated ester group. This meant that **(51)** could be converted to the protected swainsonine **(53)** in just two hydrogenation steps requiring five equivalents of hydrogen. Reduction of the azido group and the carbon-carbon double bond in **(51)**, followed by intramolecular reductive amination of the resulting amino aldehyde led to the formation of tricyclic amine **(52)**. Further hydrogenation cleaved the benzyl acetal in **(52)** and a second intramolecular reductive amination occurred giving **(53)** which was deprotected to afford (-)-swainsonine.

The overall yield of swainsonine was 26% from **(50)** or 19% from D-mannose. This represents one of the most efficient syntheses of this alkaloid.

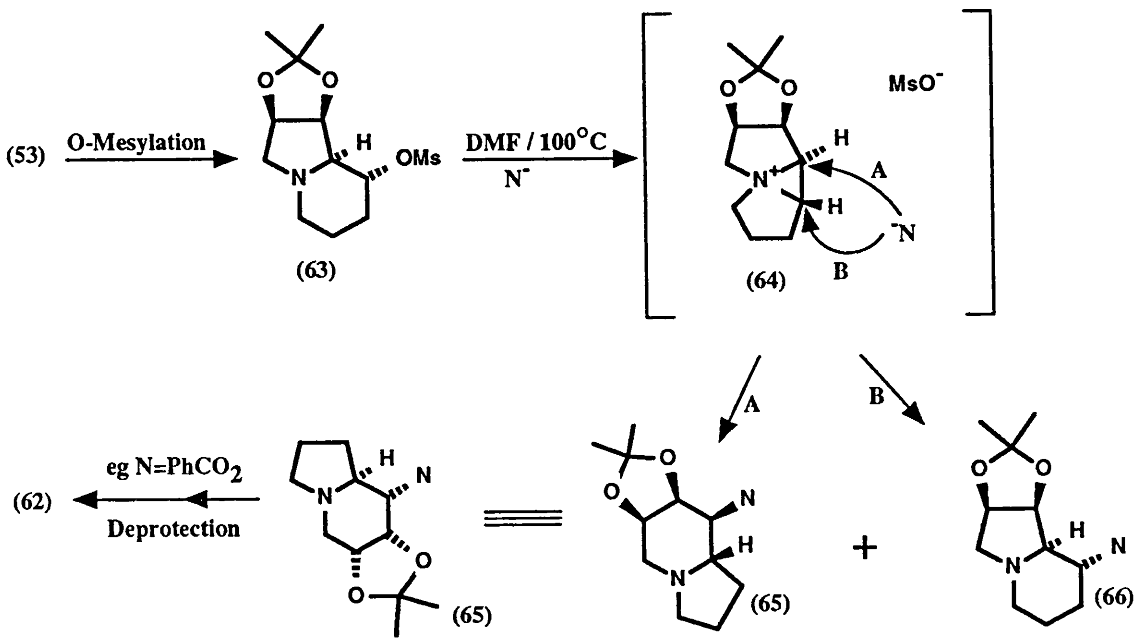

HON
OH
(54)
(i) LiAlH4
(ii) CBzCl
(iii) MsCl / py
NH
CBz
OMs
(55)
(i) TsOH aq
(ii) Amberlite IRA-400(OH⁻)
OH
NH
CBz
(56)
(i) CrO3.py2
(ii) Ph3P=CHCO2Et
NH
CBz
CO2Et
(57)
NaBH4 / CF3CH2OH
EtOH
NH
CBz
CO2Et
(i) H2 / Pd-C
(ii) Δ
H
OH
N
(58)
(i) NaBH4 / CF3CH2OH
EtOH
(ii) HCl aq
HO
OH
H
OH
N
Swainsonine

Scheme 14

Another carbohydrate-based route to this natural product has been examined by Hashimoto and coworkers.[47] (Scheme 14) Functional group manipulation of known oxime **(54)**, again derived from D-mannose, allowed access to epoxide **(57)**, *via* epoxyalcohol **(56)**. The selective hydrolysis of the di-*O*-isopropylidene intermediate **(55)** is noteworthy. These workers found that the acrylate function present in **(57)** could be effectively reduced by sodium borohydride in the presence of trifluoroethanol. Lactam **(58)** was then obtained *via* a double intramolecular cyclization of the derived amine, whereby pyrrolidine ring formation was followed by lactamization. The novel sodium borohydride/trifluoroethanol reducing system was again employed for reduction of lactam **(58)** and subsequent hydrolysis afforded (-)-swainsonine in 45% yield from **(58)** and 2.7% overall yield from **(54)**.



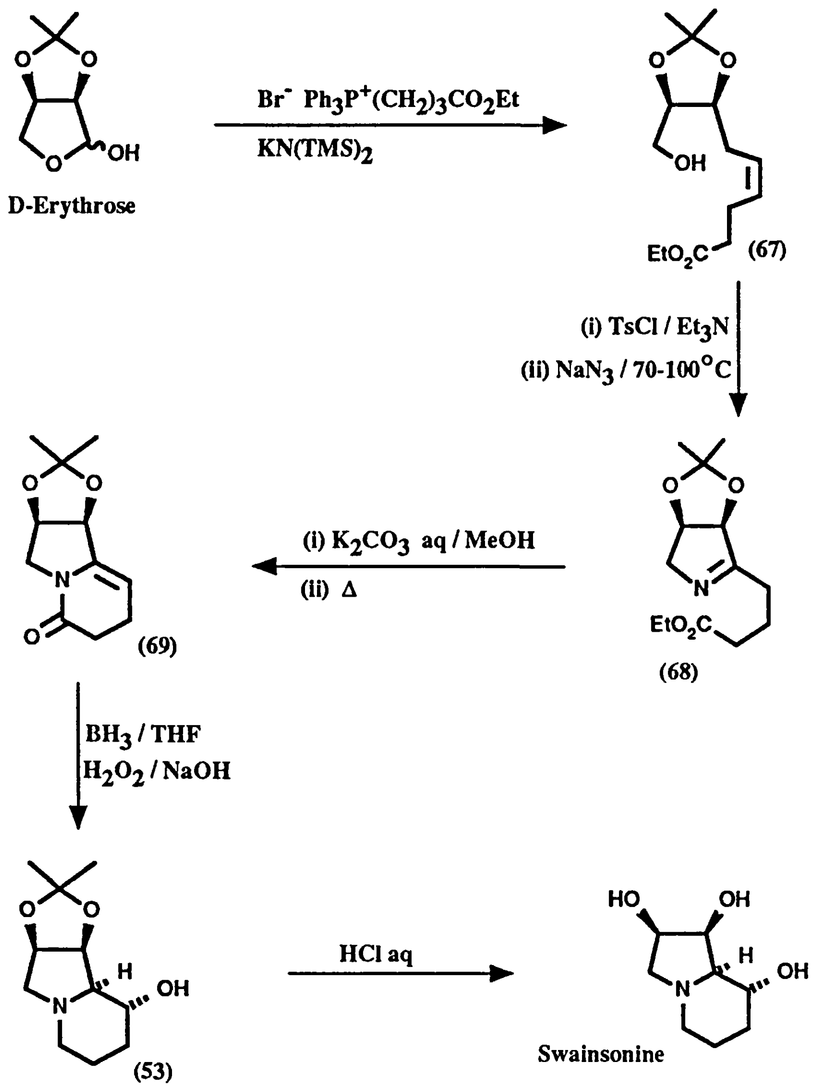
Scheme 15



Scheme 16

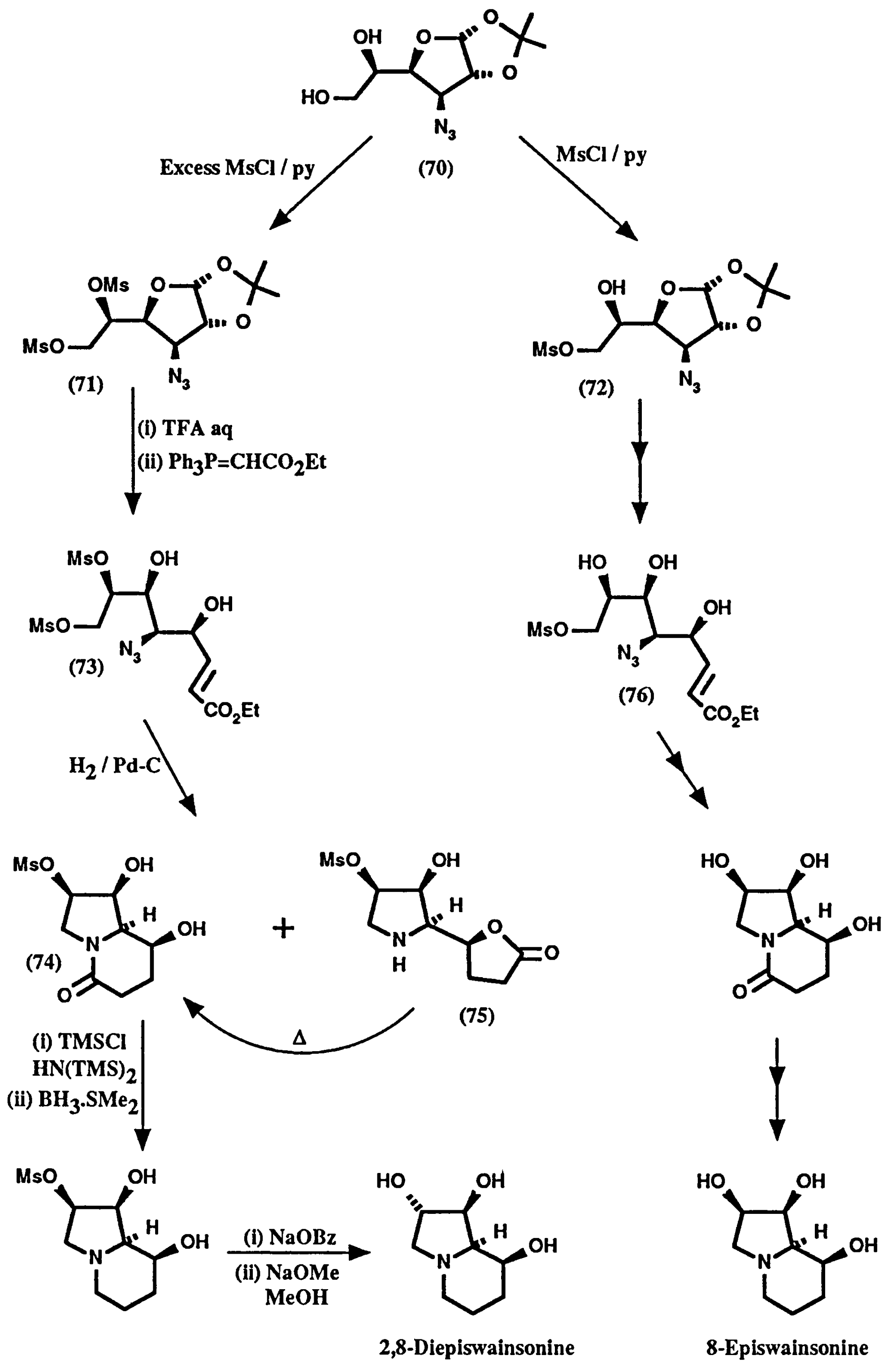
The direct conversion of an intermediate corresponding to **(57)** was achieved by use of a reductively labile nitrogen protecting group. Thus, the trifluoroacetamido derivative **(60)** was transformed into protected swainsonine **(53)** in 32% yield upon exposure to these reduction conditions. (Scheme 15) The modest yield was due to the competing formation of isomer **(61)**, isolated in 23% yield, which probably arises from attack of the nitrogen atom at the active allyl carbon. Nevertheless, deprotection of **(61)** gave a novel trihydroxyindolizidine **(62)**.

Hashimoto *et al* later discovered that nucleophilic displacement reactions on swainsonine-derived mesylate **(63)** gave mixtures of rearranged products **(65)** and swainsonine analogues **(66)**[48] (Scheme 16). These workers showed that these products arose *via* an aziridinium intermediate **(64)**, which resulted from internal displacement of mesylate by the amine function **(63)**. Using benzoate as the nucleophilic component gave a 68% yield of **(65)** (N = Bz) along with a 15% yield of 1,2-*O*-isopropylidene-8-*O*-benzoylswainsonine **(66)** (N = Bz).



Scheme 17

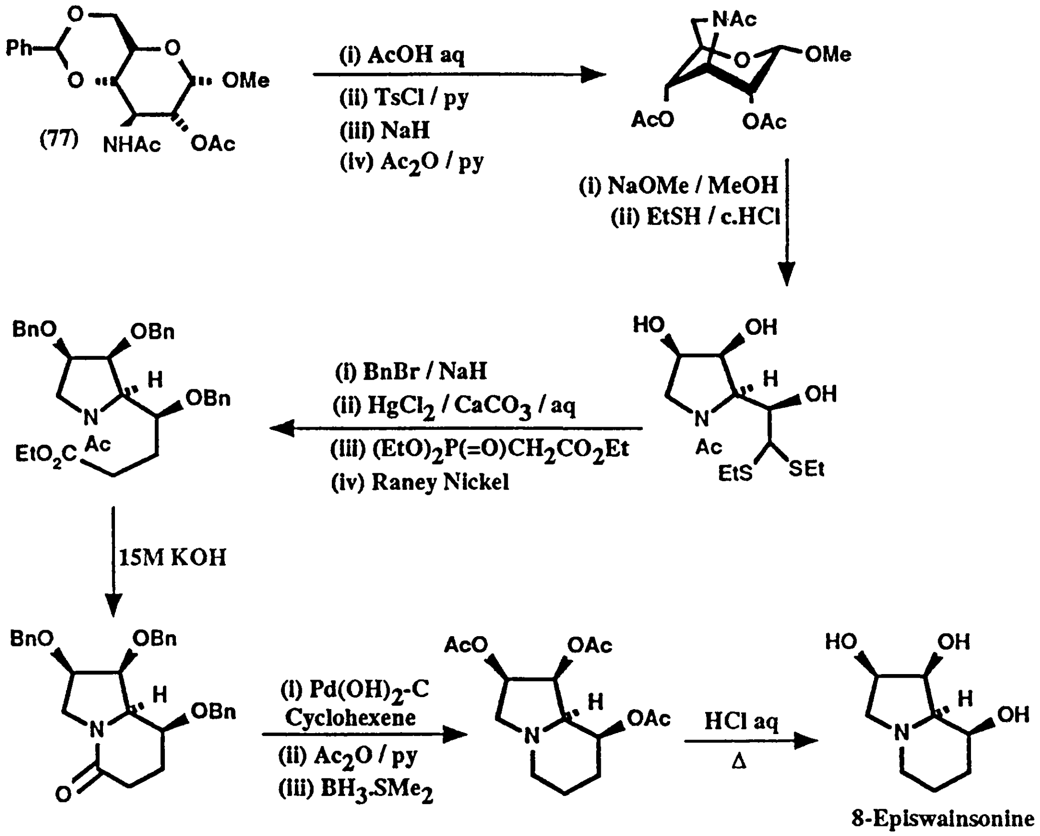
One of the shortest and most efficient syntheses of swainsonine involves an intramolecular 1,3-dipolar azide cycloaddition reaction as a key step (Scheme 17). Cha and coworkers prepared the required starting material **(67)** by a Wittig olefination of 2,3-*O*-isopropylidene-D-erythrose.[(49)] Displacement of the tosylate derived from **(67)** with azide ion and concomitant 1,3-dipolar cycloaddition to the double bond gave imino ester **(68)** directly. This was converted to enamide **(69)** *via* the free acid and stereospecific hydroboration of **(69)** afforded **(53)**, after oxidative work-up. (-)-Swainsonine was obtained by hydrolysis of **(53)** in an impressive 35% overall yield from **(67)** and 20% yield from the protected D-erythrose. In contrast to most other carbohydrate-based routes, only two of the four stereogenic centres required in the product are present in the starting material. Cha used these exisiting centres to control the face selectivity of the hydroboration reaction, which introduces the additional stereogenic centres required in stereospecific fashion.


OH
HO
N3
(70)
Excess MsCl / py
MsCl / py
OMs
MsO
(71)
OH
MsO
(72)
(i) TFA aq
(ii) Ph3P=CHCO2Et
MsO
OH
(73)
CO2Et
HO
OH
(76)
H2 / Pd-C
(74)
(75)
Δ
(i) TMSCl
HN(TMS)2
(ii) BH3.SMe2
(i) NaOBz
(ii) NaOMe
MeOH
2,8-Diepiswainsonine
8-Episwainsonine

Scheme 18

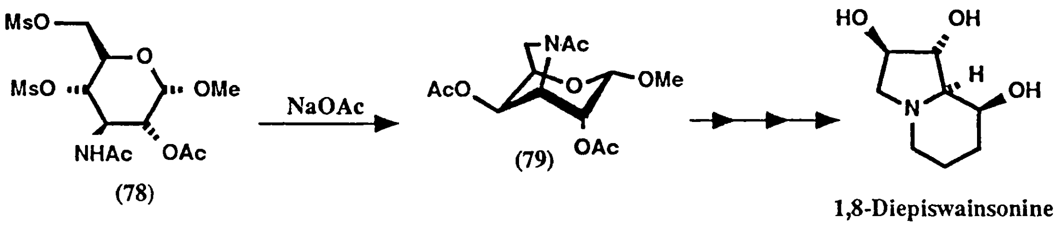
In addition to synthetic endeavours towards swainsonine itself, a number of stereoisomers have been prepared from various carbohydrate precursors. After their synthesis of swainsonine,[45] the Fujisawa group reported a route to 8-epi- and 2,8-diepiswainsonine.[50] The glucofuranose derivative **(70)**, available from D-glucose, could be either selectively monomesylated or dimesylated (Scheme 18). Hydrogenation of the unsaturated ester **(73)**, prepared from the dimesylate **(71)**, gave **(74)** *via* a double intramolecular cyclization, as well as lactone **(75)**. Thermal isomerization of **(75)** to **(74)** occurred in high yield. (+)-2,8-Diepiswainsonine was prepared in five steps from **(74)**, including a nucleophilic displacement reaction with inversion at C-2. The overall yield of this swainsonine stereoisomer from **(70)** was 1.5%.

In a similar manner, the unsaturated ester **(76)**, prepared from monomesylate **(72)**, was converted to (-)-8-episwainsonine. However, the overall yield from **(70)** was only 0.2% in this case.



(77)

Scheme 19

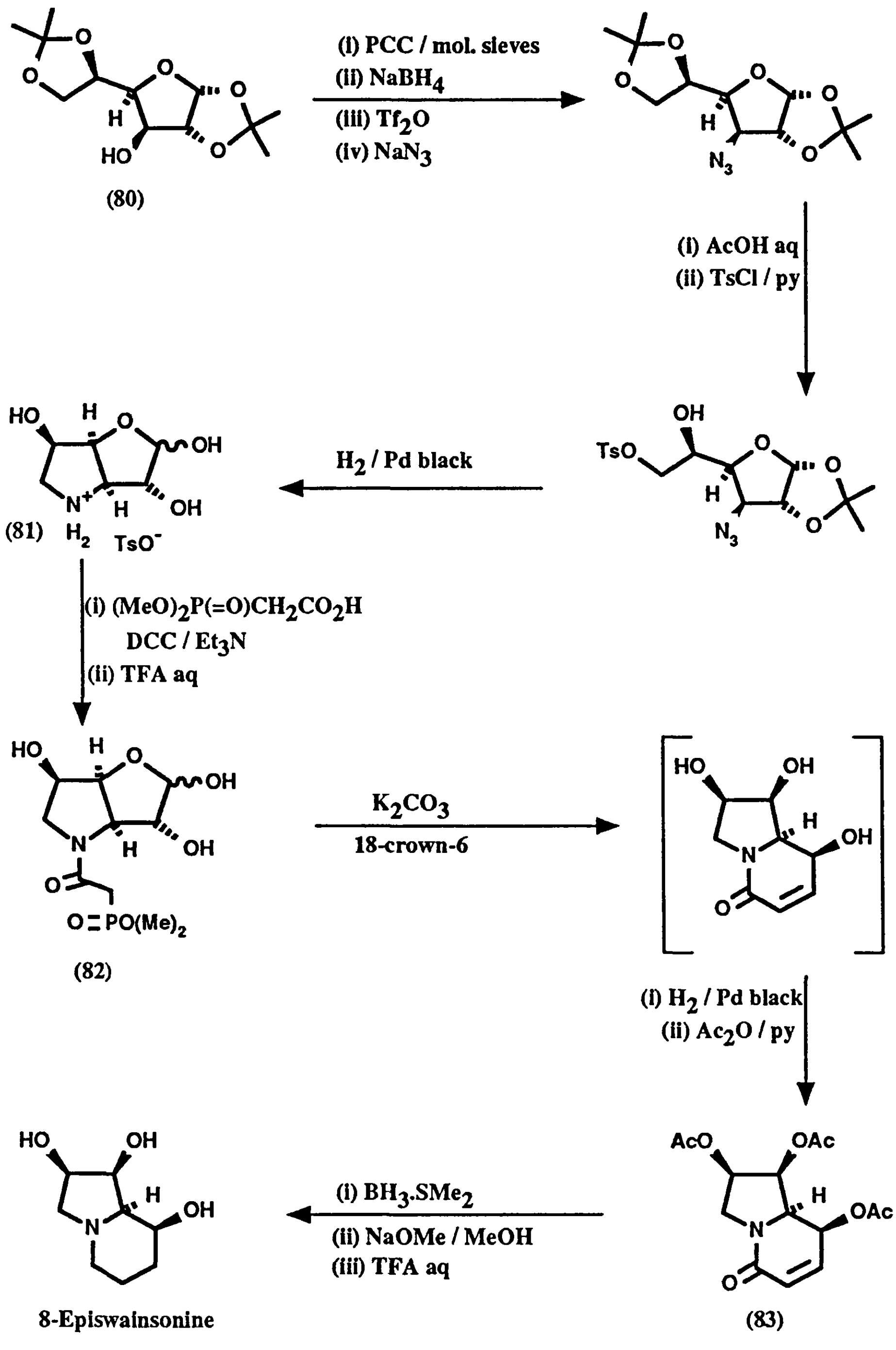


(78)

(79)

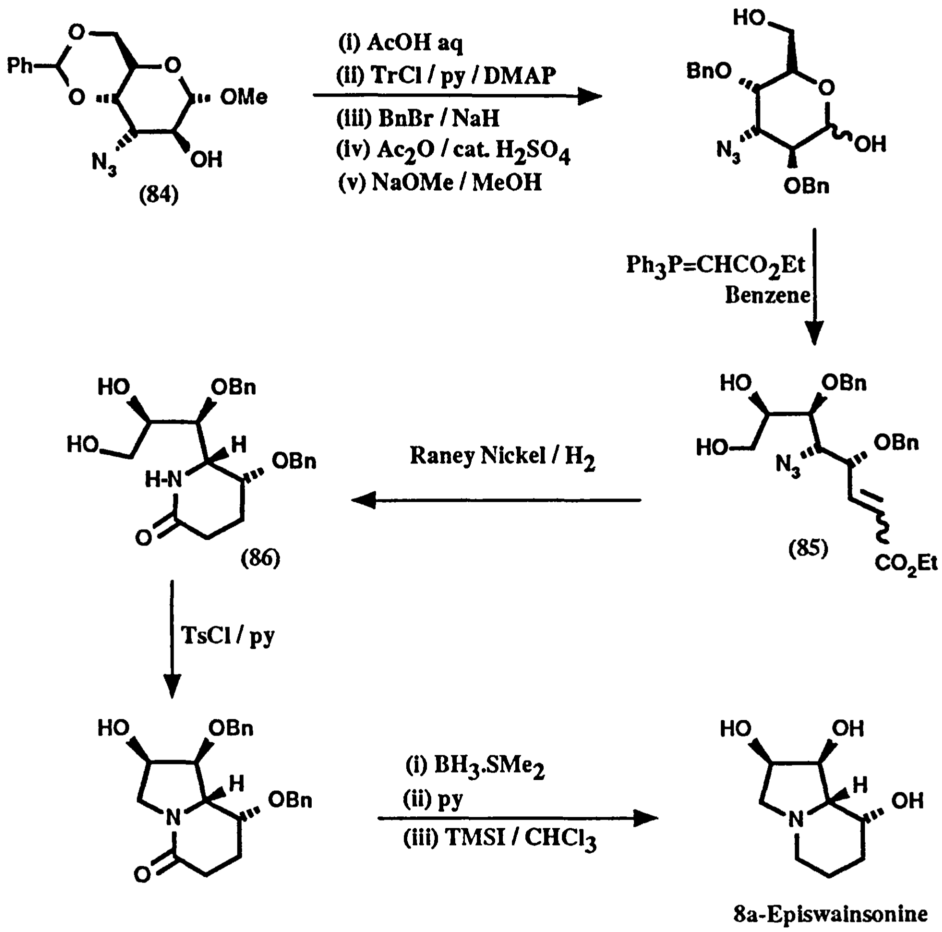
Scheme 20

A more efficient synthesis of 8-episwainsonine was later described by Tadano *et al*[51] (Scheme 19). This synthesis employed glucopyranoside **(77)**, available from D-glucose, as the starting material and the transformations involved parallel those used in Richardson's original synthesis of swainsonine[43] (see Scheme 10). (-)-8-episwainsonine was obtained in 6.7% overall yield from **(77)**. The same methodology was used to prepare (+)-1,8-diepiswainsonine in 6.7% overall yield from glucopyranoside derivative **(78)**, *via* the bicyclic galactopyranoside **(79)**[51] (Scheme 20).

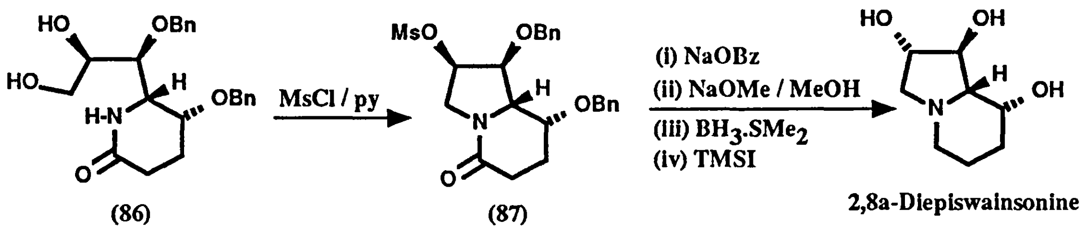

(80)
(i) PCC / mol. sieves
(ii) NaBH4
(iii) Tf2O
(iv) NaN3
(i) AcOH aq
(ii) TsCl / py
H2 / Pd black
(81)
(i) (MeO)2P(=O)CH2CO2H
DCC / Et3N
(ii) TFA aq
(82)
K2CO3
18-crown-6
(i) H2 / Pd black
(ii) Ac2O / py
(83)
(i) BH3.SMe2
(ii) NaOMe / MeOH
(iii) TFA aq
8-Episwainsonine

Scheme 21

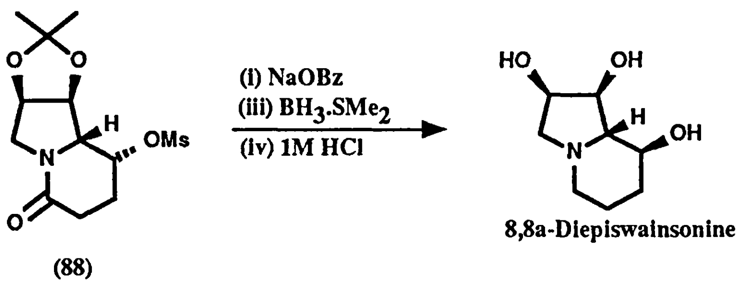
Fleet has published an improved synthesis of 8-episwainsonine from the versatile glucofuranose intermediate **(81)**, which was prepared from diacetone glucose **(80)** in 53% overall yield (Scheme 21).[52] The key step was an intramolecular Wadsworth-Horner-Emmons reaction on lactol **(82)**, which gave indolizidinone **(83)** after reduction of the intermediate unsaturated lactam followed by *O*-acetylation. This may be regarded as the intramolecular variant of the olefination reaction used in previous trihydroxyindolizidine syntheses (e.g. Scheme 10). (-)-8-episwainsonine was derived from **(83)** and the overall yield from **(80)** was nearly 14%.



Scheme 22



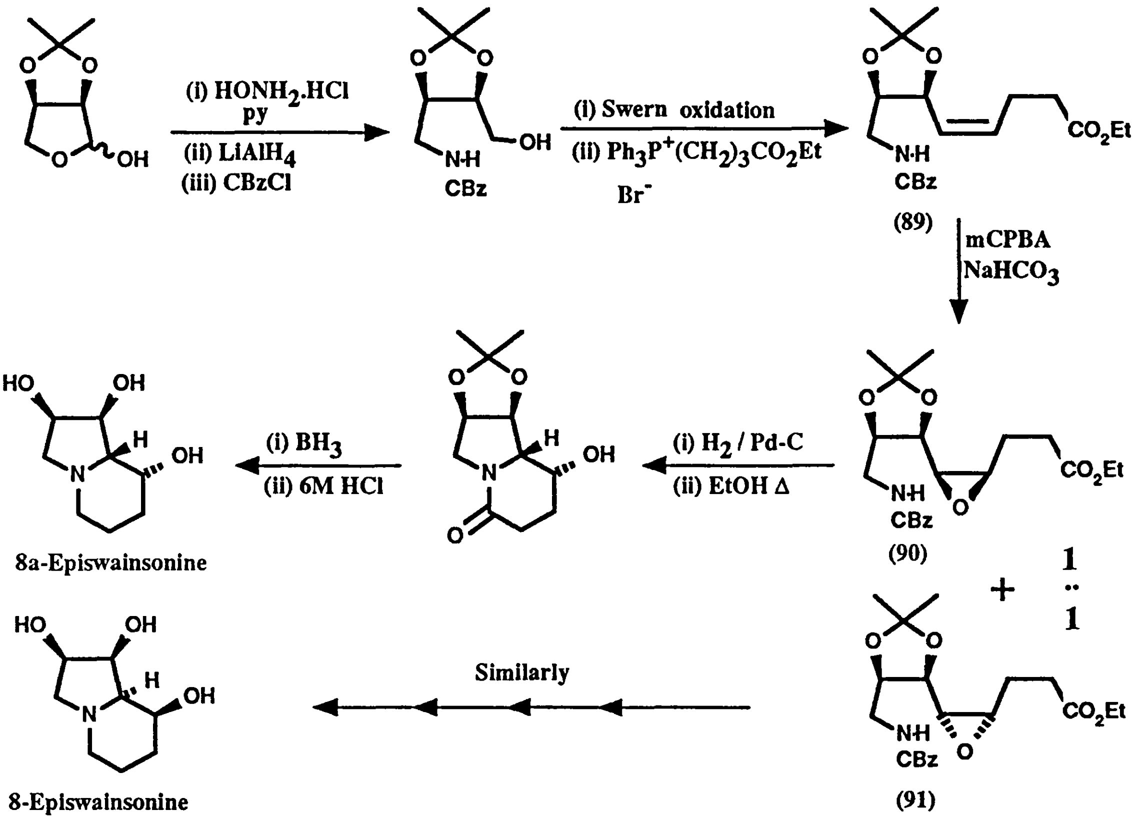
Scheme 23



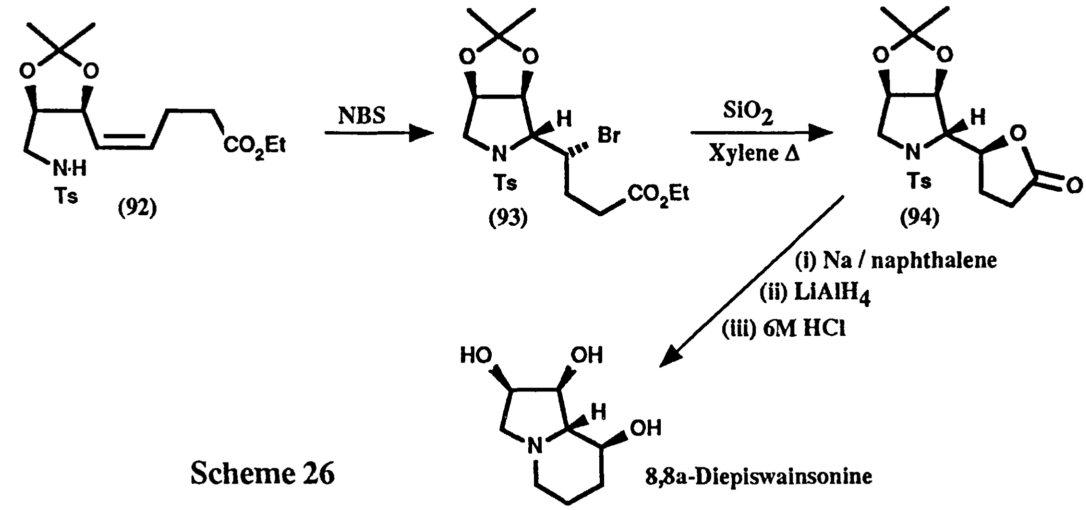
Scheme 24

Three further stereoisomers of swainsonine have been synthesized by the Tadano group. Altropyranoside **(84)**, prepared from D-glucose, was converted to the unsaturated ester **(85)** as shown in Scheme 22.(53) This intermediate is analogous to those prepared by the Fujisawa group (see Scheme 18). However, in this case the terminal hydroxyl group was not activated as a leaving group and so hydrogenation of **(85)** led exclusively to formation of the piperidinone **(86)**. A subsequent cyclization gave the 5,6-fused bicycle which was reduced and deprotected to give (-)-8a-episwainsonine. The overall yield from **(84)** was approximately 9%.

The piperidinone intermediate **(86)** could also be converted to (-)-2,8a-diepiswainsonine *via* mesylate **(87)**, which suffered inversion of stereochemistry at C-2 *en route* to the final product (Scheme 23), and an overall yield of 5.3% from **(84)** was realized.(54) Displacement of mesylate with inversion was again employed as a means of converting indolizidinone **(88)**, prepared from **(84)** using alternative oxygen protection, to (-)-8,8a-diepiswainsonine (Scheme 24). This isomer was obtained in approximately 8% overall yield from **(84)**.(54)



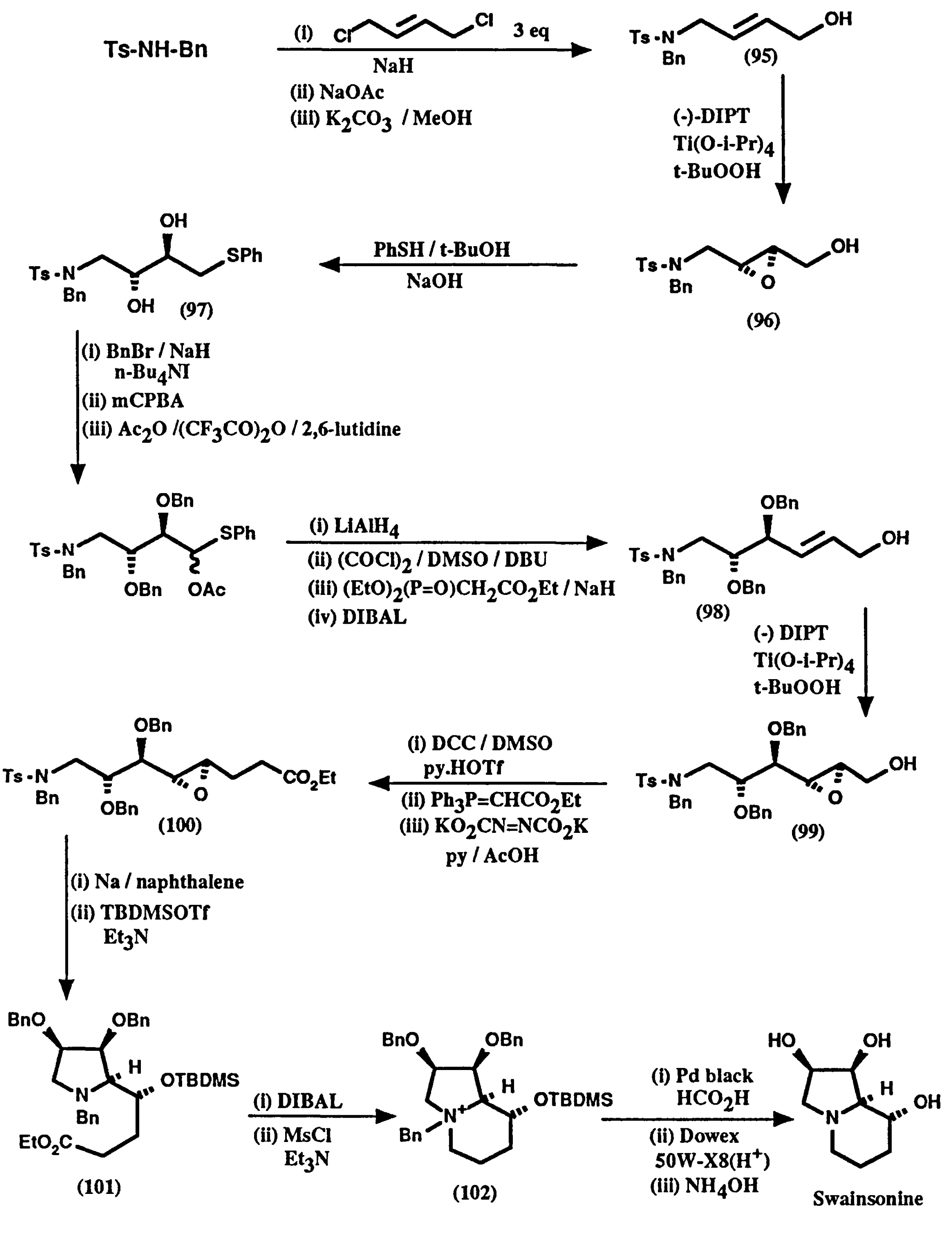
Scheme 25



Scheme 26

Other synthetic studies in this area by Cha *et al* led to divergent routes to some of these compounds. As in their concise synthesis of swainsonine (see Scheme 17), these workers used a protected D-erythrose to prepare the required intermediates.[(55)] Thus, Z-alkene **(89)** was prepared in two steps and 50-60% overall yield (Scheme 25). Epoxidation of **(89)** gave a 1:1 mixture of diastereomeric epoxides **(90)** and **(91)** which were readily separated by chromatography. The method by which these epoxides were converted to trihydroxyindolizidines was essentially the same as that employed by Hashimoto[(47)] (see Scheme 14). (-)-8a-episwainsonine was obtained from **(90)** whereas (91) provided the (-)-8-epi isomer. Finally, (-)-8, 8a-diepiswainsonine was synthesized from the *N*-tosyl alkene **(92)** *via* a moderately selective haloamidation reaction which afforded **(93)** as the major product, together with its diastereoisomer (4:1 selectivity) (Scheme 26). Separation of this mixture was achieved by lactonization, whereupon **(93)** reacted much faster than its diastereoisomer giving uncontaminated lactone **(94)**. The trihydroxyindolizidine was obtained in three steps from **(94)**. The overall yields of 8a-epi-, 8-epi- and 8,8a-diepiswainsonine from these routes were approximately 10, 10 and 4% respectively, from the protected D-erythrose.

Biological evaluation of the various swainsonine stereoisomers for glycosidase inhibitory activity has revealed that, on the whole, changes in stereochemistry leads to reduced activity. For example, the inhibitory effect of (-)-8-epi- and (+)-1,8-diepiswainsonine against α-D-mannosidase is approximately 20% that of swainsonine,[(51)] and (-)-2,8a-diepiswainsonine does not inhibit this enzyme to any appreciable extent.[(54)] However, (-)-8,8a-diepiswainsonine was found to be a reasonably potent inhibitor of α-D-mannosidase[(54)] and the activity of the (-)-8a-epi-isomer against this enzyme was found to approach that of swainsonine itself.[(53b)]

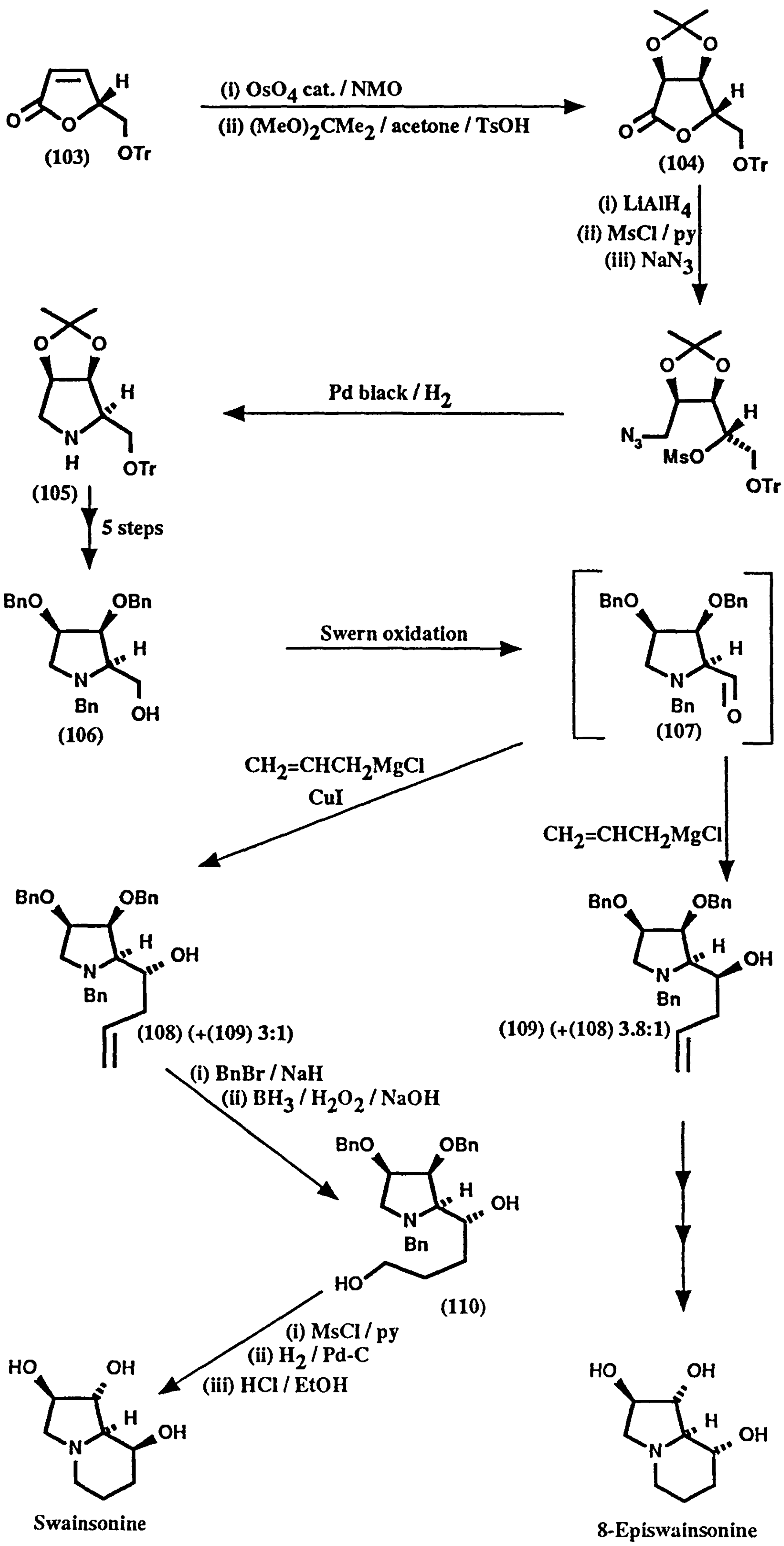


Scheme 27

2.2.2.2 Synthesis from Non-Carbohydrate Precursors

An early synthesis of swainsonine was described by Sharpless and coworkers which made use of the highly successful asymmetric epoxidation reaction[56]. The iterative process used is outlined in Scheme 27. Epoxidation of allylic alcohol **(95)** according to the standard conditions developed by Sharpless gave epoxy alcohol **(96)** in 95% enantiomeric excess. Treatment of **(96)** with phenylthiolate ion under basic conditions led to formation of diol **(97)** *via* a base-catalyzed Payne rearrangement. The conversion of **(97)** to allylic alcohol **(98)** was accomplished in seven steps and asymmetric epoxidation of **(98)** afforded epoxy alcohol **(99)** as a single diastereoisomer. The carbon-backbone of **(99)** was extended to provide the epoxy ester **(100)**. When this material was treated with sodium naphthalenide, the tosyl group was removed and the intermediate epoxy amine cyclized to give, after hydroxyl-group protection, the pyrrolidine **(101)**. Formation of the 5,6-fused ring system was achieved by mesylation of the alcohol derived from **(101)** which provided the quaternary ammonium salt **(102)**. This material was converted to (-)-swainsonine (overall yield 6.6% from *N*-benzyl-p-toluenesulphonamide). This synthesis represents the first non-carbohydrate based route to swainsonine, and although the synthesis is linear, it is unambiguous. Since the stereogenic centres of the product are introduced *via* stereoregulated reactions, the synthesis allows for stereochemical variations throughout, and in principle, all sixteen stereoisomers of swainsonine could be prepared using this methodology.

Sharpless has reported the synthesis of 2-epi- and 2,8-diepiswainsonine using modifications of this route.[57] In contrast to the parent compound, both of these isomers were found to be inactive with respect to jack bean α-mannosidase inhibition. 2-Episwainsonine exhibited

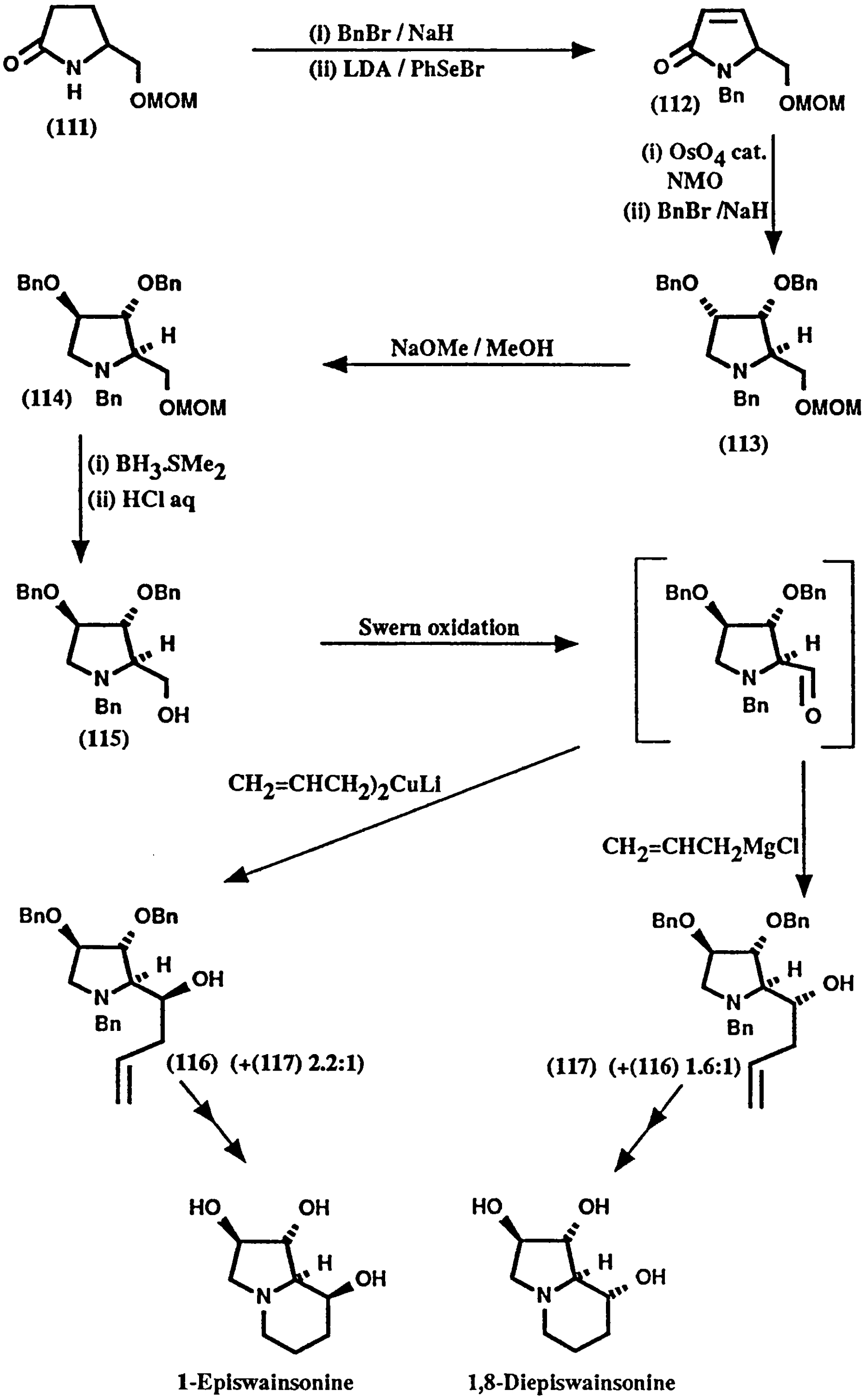


(i) OsO4 cat. / NMO
(ii) (MeO)2CMe2 / acetone / TsOH
(103)
(104)
(i) LiAlH4
(ii) MsCl / py
(iii) NaN3
Pd black / H2
(105)
5 steps
(106)
Swern oxidation
(107)
CH2=CHCH2MgCl
CuI
CH2=CHCH2MgCl
(108) (+(109) 3:1)
(109) (+(108) 3.8:1)
(i) BnBr / NaH
(ii) BH3 / H2O2 / NaOH
(110)
(i) MsCl / py
(ii) H2 / Pd-C
(iii) HCl / EtOH
Swainsonine
8-Episwainsonine

Scheme 28

moderate α-glucosidase inhibitory activity and 2,8-diepiswainsonine was a weak inhibitor of β-glucosidase. When tested against the glycoprotein processing glycosidases, 2-episwainsonine proved to be similar to the parent compound in that it inhibited mannosidase II, whereas the 2,8-diepi-isomer was inactive.[57]

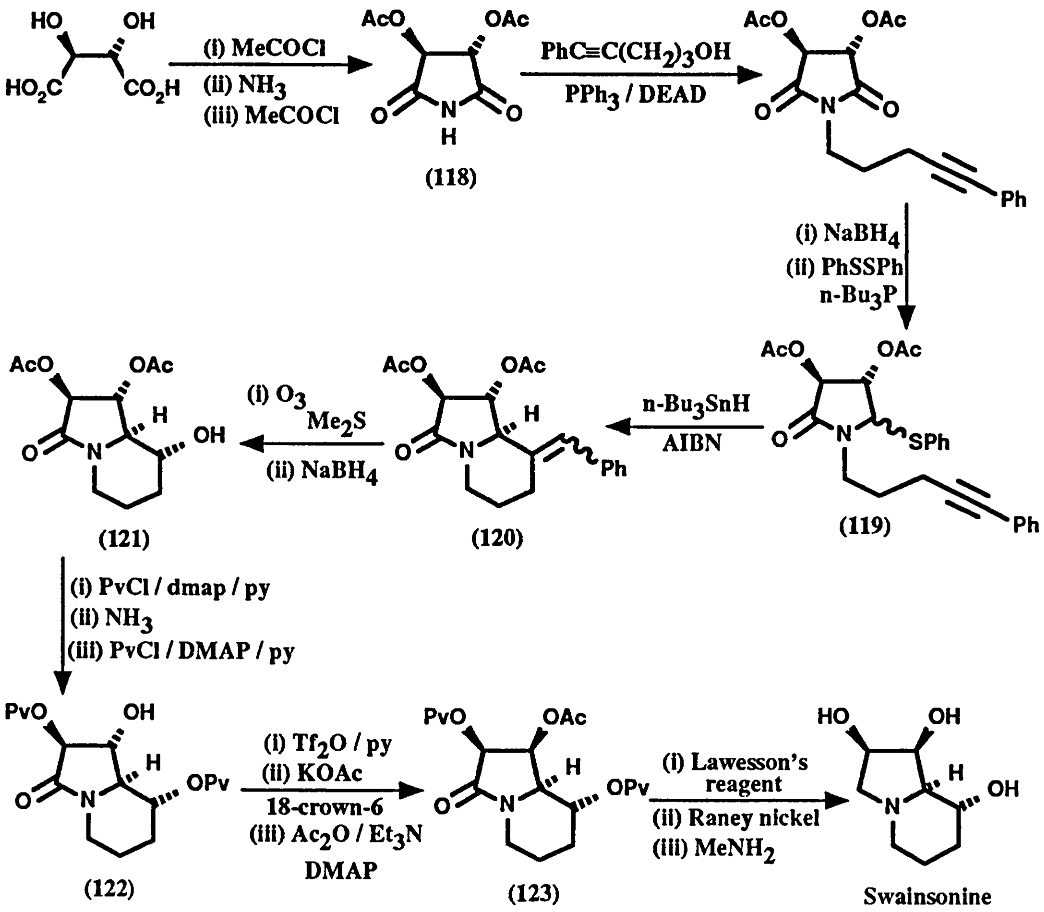
Another non-carbohydrate based synthesis of swainsonine and its 8-epi-isomer was described by Ikota and Hanaki.[58] These workers used the optically active butenolide **(103)**, prepared from (R)-glutamic acid, as the starting material (Scheme 28). *cis*-Dihydroxylation of **(103)** followed by ketalization gave lactone **(104)** as a single diastereoisomer which was converted to pyrrolidine **(105)**. The tribenzyl derivative **(106)** was obtained in five steps from **(105)**. Swern oxidation of the primary alcohol group in **(105)** yielded a sensitive aldehyde **(107)** which was condensed with an organocopper reagent to give alcohol **(108)** as the major product (3:1 separable mixture of diastereoisomers). When the corresponding Grignard reagent was condensed with **(107)**, the opposite selectivity was observed and **(109)** was obtained as the major product (3.8:1 separable mixture of diastereoisomers). Protection of the hydroxyl group of **(108)** followed by hydroboration of the double bond afforded primary alcohol **(110)** and this was converted to (-)-swainsonine *via* a bicyclic quaternary ammonium salt, in a manner comparable to that employed by Sharpless in the previous synthesis (see Scheme 27). A parallel series of reactions transformed **(109)** into (-)-8-episwainsonine. The overall yield of each isomer was less than 1% from **(103)**. However, the approach incorporates a degree of flexibility in that two isomeric products may be synthesized in a selective manner from a common intermediate. Furthermore, it is noteworthy that the starting material contains only one stereogenic centre.



(i) BnBr / NaH
(ii) LDA / PhSeBr
(111)
(112)
(i) OsO_4 cat.
NMO
(ii) BnBr /NaH
NaOMe / MeOH
(113)
(114)
(i) $BH_3.SMe_2$
(ii) HCl aq
(115)
Swern oxidation
CH_2=$CHCH_2)_2CuLi$
CH_2=$CHCH_2MgCl$
(116) (+(117) 2.2:1)
(117) (+(116) 1.6:1)
1-Episwainsonine
1,8-Diepiswainsonine

Scheme 29

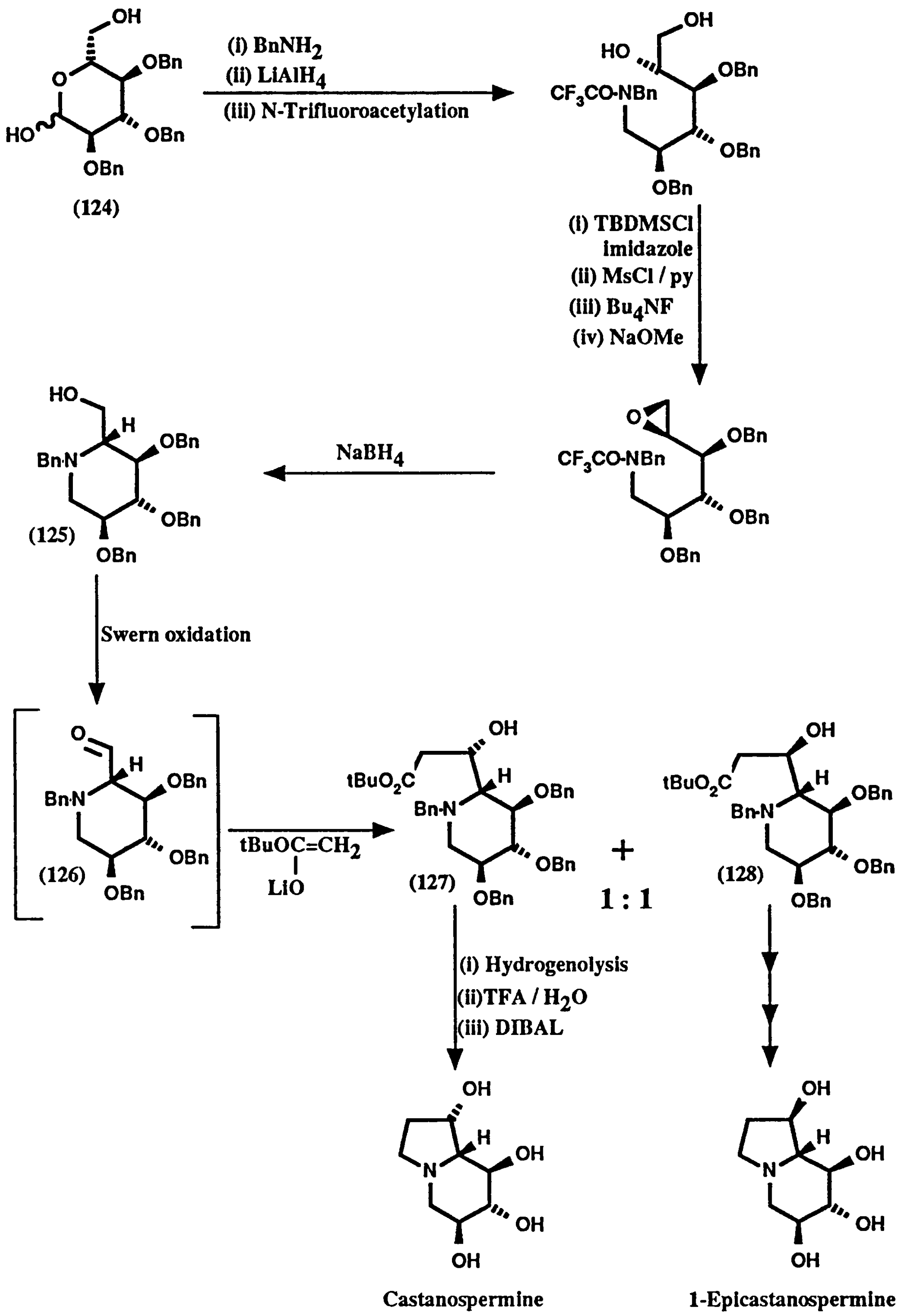
These workers have also prepared 1-epi- and 1,8-diepiswainsonine using related chemistry.[59] In this case lactam **(111)**, prepared from (S)-glutamic acid, was converted to the unsaturated derivative **(112)** (Scheme 29). *cis*-Dihydroxylation of **(112)** again proceeded in a stereospecific fashion to give, after *O*-benzylation, the lactam **(113)**. Base-catalyzed epimerization of **(113)** afforded the *trans*-3,4-disubstituted derivative **(114)** from which the primary alcohol **(115)** was prepared *via* reduction and hydrolysis. As in the previous route, the synthesis of the indolizidines was based on the allylation of the aldehyde obtained from oxidation of **(115)**. The adducts **(116)** and **(117)** were converted to (-)-1-epi- and (+)-1,8-diepiswainsonine respectively using the same transformations as those depicted in Scheme 28 (overall yields from **(111)**: 1-episwainsonine, 2.7%; 1,8-diepiswainsonine, 3.2%). An improved route to alcohol **(115)** from a carbohydrate derivative was subsequently reported by these workers.[60]



Scheme 30

A synthesis of swainsonine from has been accomplished by Hart and his associates involving α-acylamino radical cyclizations.[61] The radical precursor **(119)** was prepared in three steps from imide **(118)** which is readily available from D-tartaric acid (Scheme 30). When **(119)** was subjected to typical radical cyclization conditions indolizidinone **(120)** was obtained as a mixture of E/Z isomers. Oxidative cleavage of the benzylidene moiety in **(120)**, followed by reduction of the resulting ketone afforded alcohol **(121)** from which the di-*O*-pivalate **(122)** could be prepared. The conversion of **(121)** to **(122)** was accompanied by formation of the tri-*O*-pivalate as a minor product. The requisite inversion of stereochemistry at C-1 was achieved by performing a nucleophilic displacement reaction on the triflate derived from **(122)**. The synthesis of (-)-swainsonine was then completed in a straightforward manner from acetoxy indolizidinone **(123)** (overall yield: 14% from **(118)**; 6.7% from D-tartaric acid).

Modifications to this route could provide access to a number of stereoisomeric indolizidinetriols. This was exemplified by the reduction of **(121)** with lithium aluminium hydride which gave 1-episwainsonine in 25% yield.



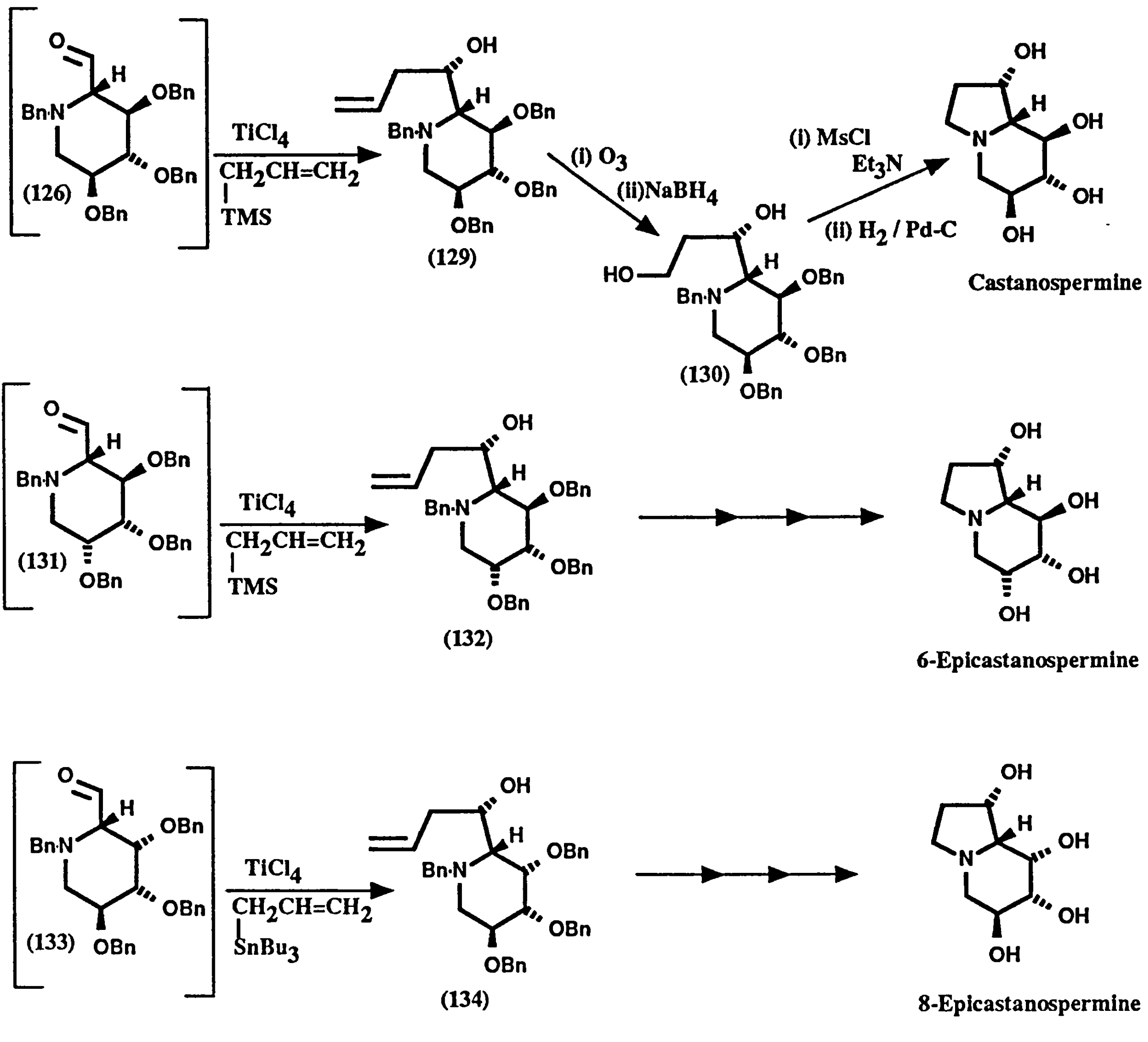
(124)
(i) BnNH2
(ii) LiAlH4
(iii) N-Trifluoroacetylation
(i) TBDMSCl imidazole
(ii) MsCl / py
(iii) Bu4NF
(iv) NaOMe
NaBH4
(125)
Swern oxidation
(126)
tBuOC=CH2
LiO
(127)
(128)
1 : 1
(i) Hydrogenolysis
(ii)TFA / H2O
(iii) DIBAL
Castanospermine
1-Epicastanospermine

Scheme 31

2.3 The Synthesis of Tetrahydroxyindolizidines

2.3.1 Syntheses from Carbohydrate Precursors

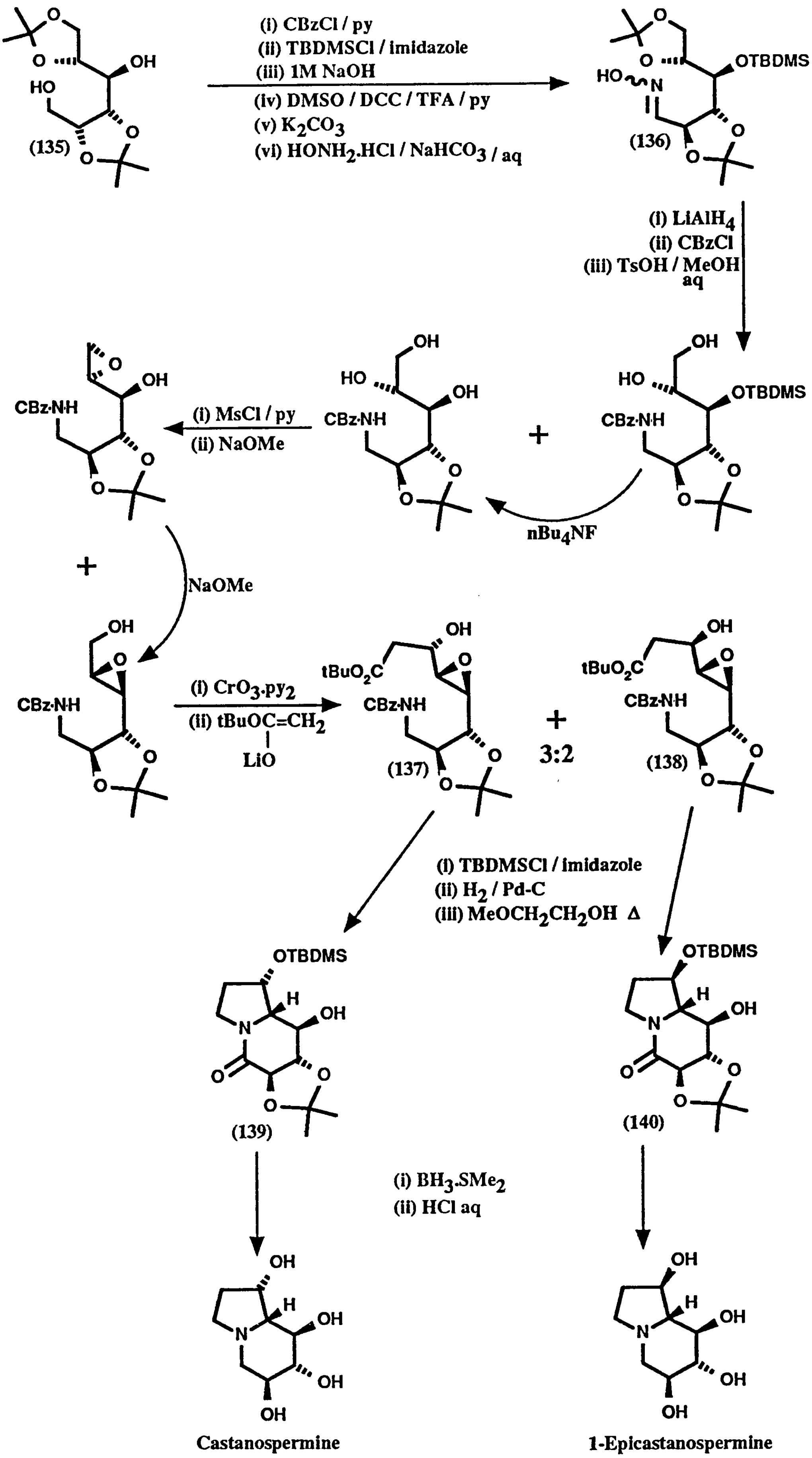
The first total synthesis of the tetrahydroxyindolizidine castanospermine was reported by Ganem and Bernotas.[62] In this synthesis, which also provided 1-epicastanospermine, the non-selective addition of lithio *tert*-butylacetate to a chiral aldehyde **(126)** furnished two separable adducts **(127)** and **(128)** which could be transformed into (+)-castanospermine and (-)-1-epicastanospermine respectively (Scheme 31). The chiral aldehyde **(126)** was obtained in nine steps from 2,3,4-tri-*O*-benzyl-D-glucopyranose **(124)** which was readily available from D-glucose. The formation of piperidine **(125)** was accompanied by the production of significant amounts of an azepane derivative, resulting from intramolecular cyclization of the intermediate amino epoxide *via* attack of the amino group at the terminal epoxide centre.



TiCl4
CH2CH=CH2
TMS
(126)
(129)
(i) O3
(ii)NaBH4
(130)
(i) MsCl
Et3N
(ii) H2 / Pd-C
Castanospermine
(131)
(132)
6-Epicastanospermine
(133)
SnBu3
(134)
8-Epicastanospermine

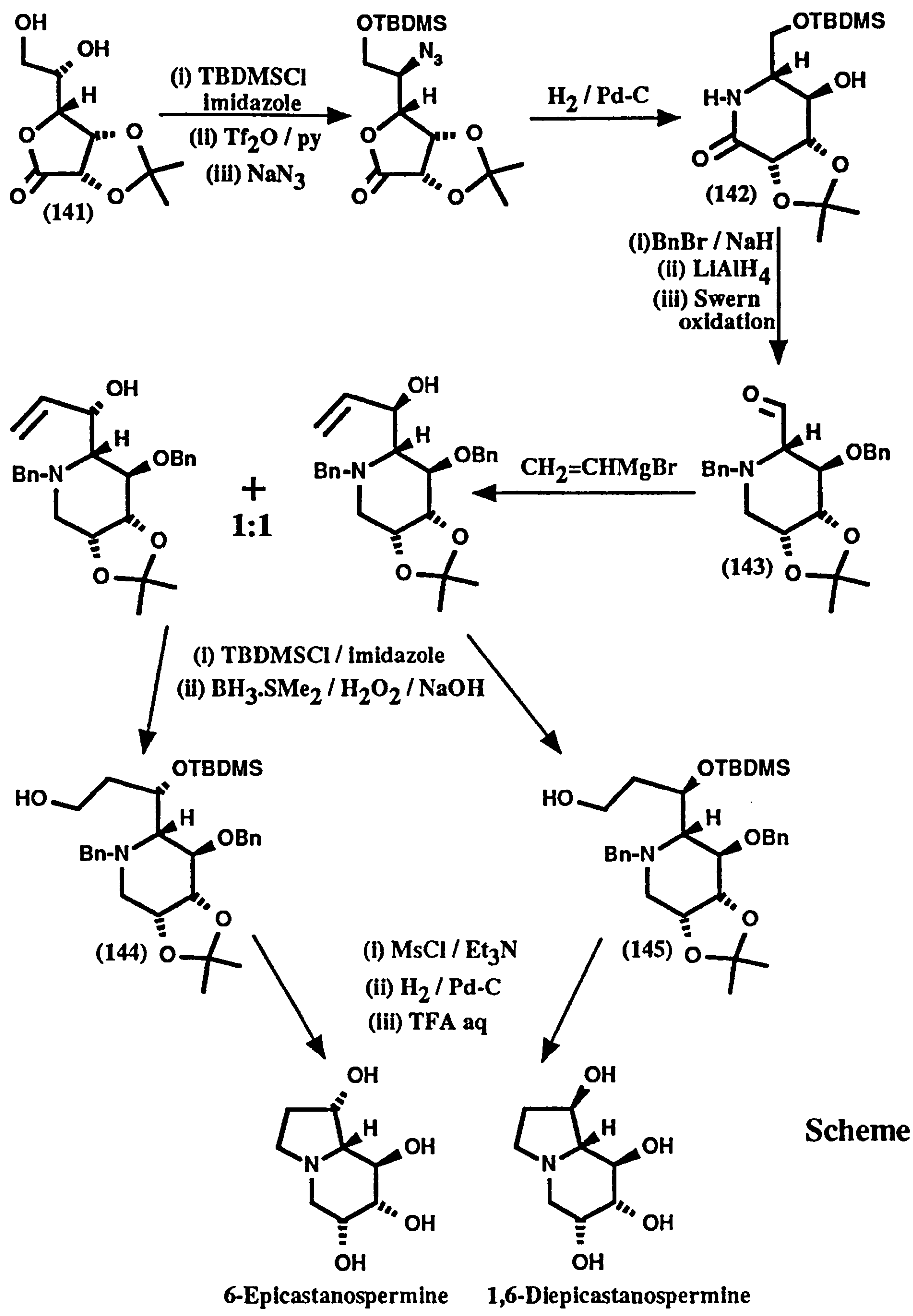
Scheme 32

Ganem published subsequently with Ikota and Hamana on the selective allylation (see Schemes 28 and 29) of aldehyde **(126)** in an improved synthesis of castanospermine[63] (Scheme 32). Chelation controlled allylation of **(126)** afforded **(129)** (>95:<5 diastereomer ratio by ^{1}H nmr). Ozonolysis of **(129)** followed by reduction gave the amino alcohol **(130)** which was selectively monomesylated to give, after exhaustive hydrogenolysis, (+)-castanospermine, presumably *via* a quaternary ammonium salt (see Schemes 27, 28 and 29). The alkaloid was obtained in some 19% overall yield from methyl-α-D-glucopyranoside. In addition to the allylation of aza-gluco aldehyde **(126)**, the Lewis acid mediated allylation of aza-manno and aza-galacto aldehydes **(131)**[64] and **(133)**[65] was also investigated. Under the conditions shown in Scheme 32, allylation of **(131)** and **(133)** produced adducts **(132)** and **(134)** respectively, in greater than 90% diastereomeric excess. Conversion of **(132)** to 6-epicastanospermine and **(134)** to 8-epicastanospermine was achieved by a series of steps which paralleled the conversion of **(129)** to castanospermine (overall yields: 6-epicastanospermine, 27% from **(131)**; 8-epicastanospermine, 55% from (134)). This represents the first total synthesis of the natural product 6-epicastanospermine (erroneous conclusions concerning the absolute stereochemistry of the natural product were subsequently shown to be the result of misleading chiroptical data for the synthetic material, see Schemes 34 and 35, Fleet *et al.*[67b])

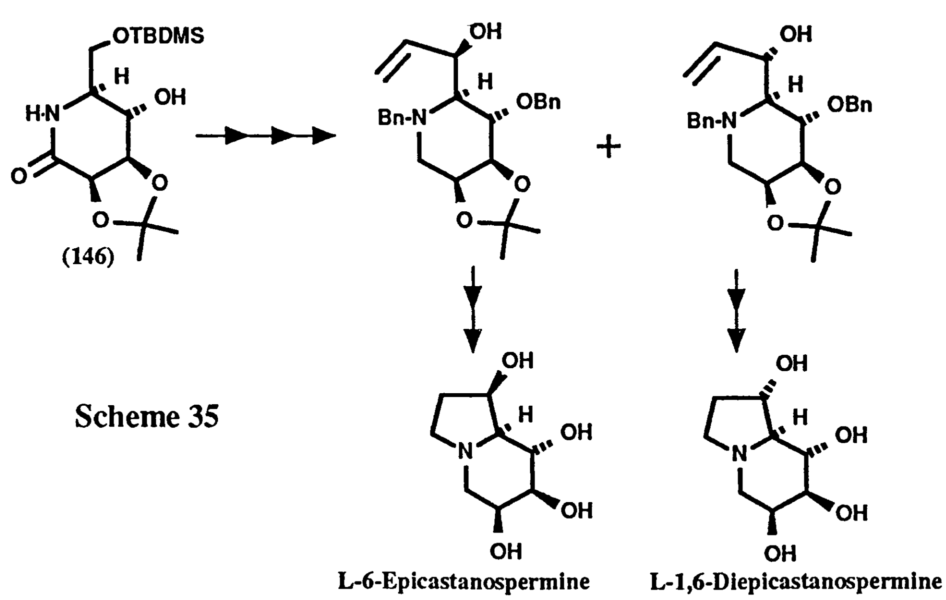

(i) CBzCl / py
(ii) TBDMSCl / imidazole
(iii) 1M NaOH
(iv) DMSO / DCC / TFA / py
(v) K_2CO_3
(vi) $HONH_2.HCl$ / $NaHCO_3$ / aq
(135)
(136)
(i) $LiAlH_4$
(ii) CBzCl
(iii) TsOH / MeOH aq
nBu_4NF
(i) MsCl / py
(ii) NaOMe
NaOMe
(i) $CrO_3.py_2$
(ii) $tBuOC=CH_2$ LiO
3:2
(137)
(138)
(i) TBDMSCl / imidazole
(ii) H_2 / Pd-C
(iii) $MeOCH_2CH_2OH$ Δ
(139)
(140)
(i) $BH_3.SMe_2$
(ii) HCl aq
Castanospermine
1-Epicastanospermine

Scheme 33

The synthesis of castanospermine and 1-epicastanospermine from D-mannose was also accomplished by Hashimoto and coworkers.[66] The key step in this route was the double intramolecular cyclization of the epoxy amino esters obtained from **(137)** and **(138)** (Scheme 33). A related strategy was employed by these workers in their synthesis of swainsonine (see Scheme 14). However, in this case, the *O*-isopropylidene protection of the 6,7-trans-diol in **(137)** and **(138)** restricts the orientation of the intermediate aminomethyl moiety such that piperidine ring closure occurs first, followed by lactamization. The key intermediates **(137)** and **(138)** were prepared as a 3:2 mixture which was subjected to the double cyclization conditions to give a corresponding mixture of indolizidinones **(139)** and **(140)**. After chromatographic separation, **(139)** and **(140)** were converted to (+)-castanospermine and (-)-1-epicastanospermine respectively (overall yields: < 1%). One notable feature of this route is the base-catalyzed epimerization of an aldehyde derived from diol **(135)** (prepared from D-mannose) *en route* to the oxime intermediate **(136)**, required for the preparation of **(137)** and **(138)**.

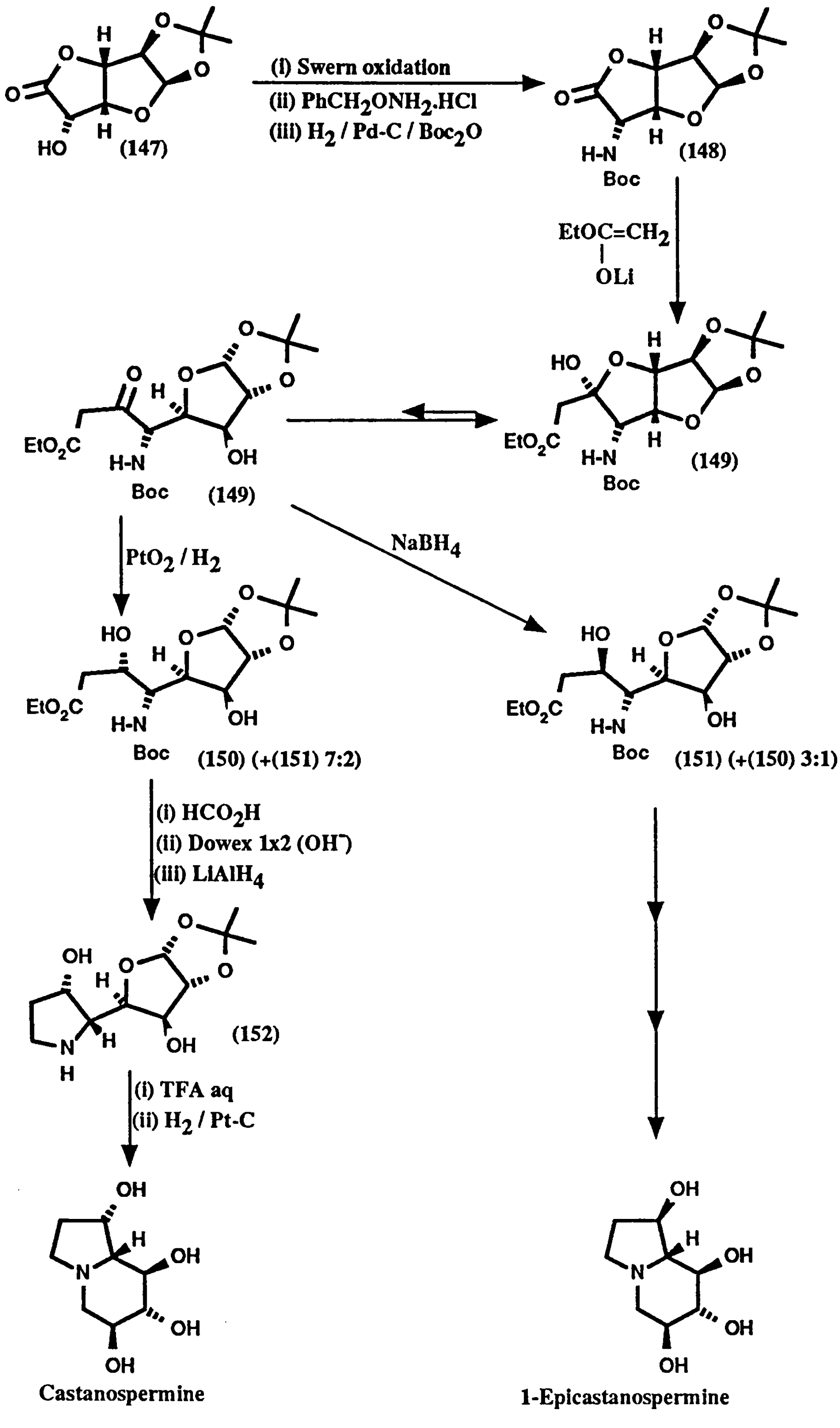


Scheme 34



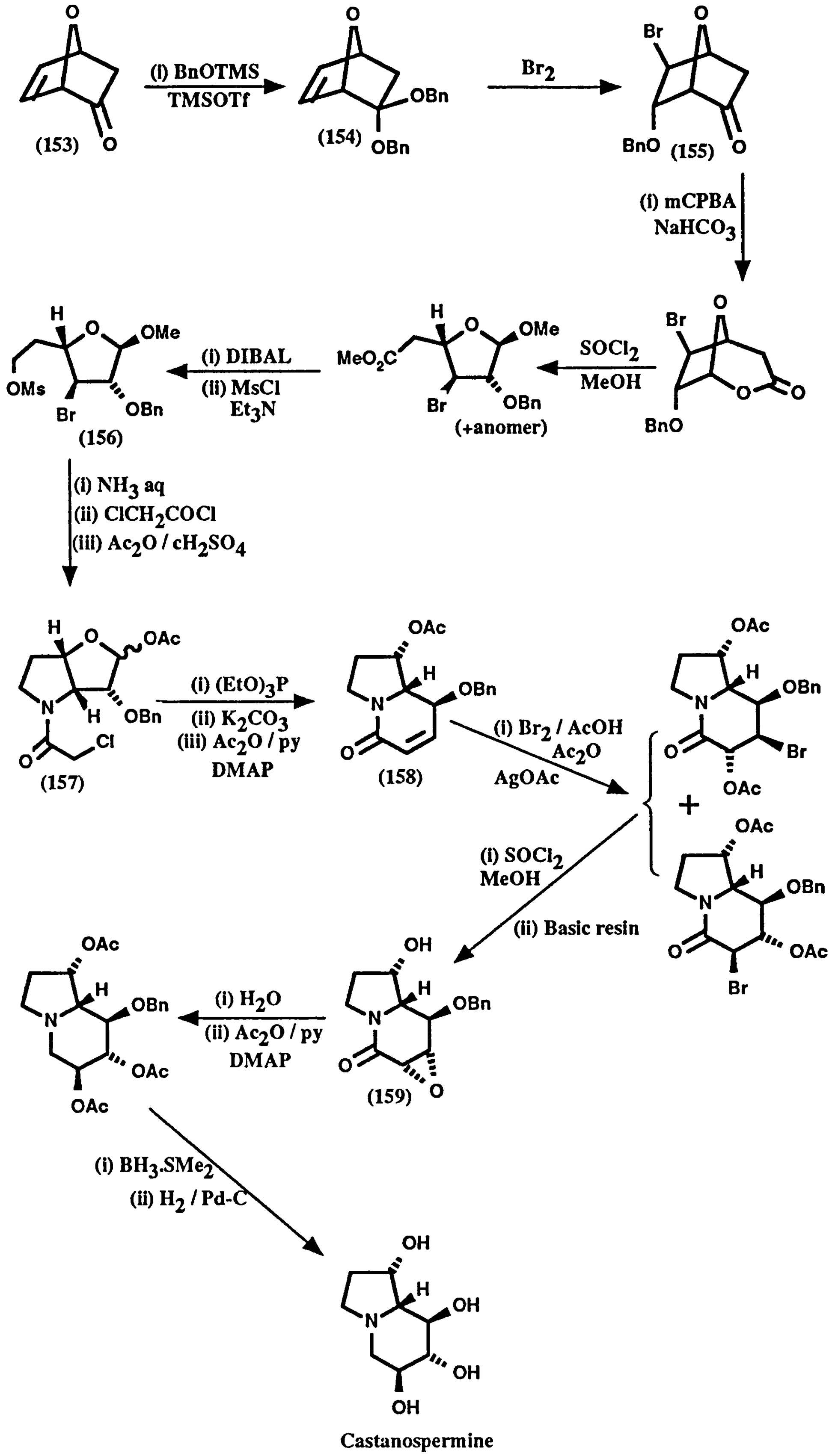
Scheme 35

The use of carbohydrate-based starting materials for the synthesis of stereoisomers of castanospermine has been demonstrated by Fleet and coworkers.[67] This group has shown that both L- and D-gulonolactone are versatile precursors to a range of aza-sugar derivatives.[68] The synthesis of 6-epi- and 1,6-diepicastanospermine was described, starting from a partially protected L-gulonolactone derivative **(141)** which was converted to lactam **(142)** in four steps[68a,b] (approximately 30% from L-gulonolactone) (Scheme 34). Non-selective addition of a vinyl Grignard reagent to aldehyde **(143)**, prepared in three steps from **(142)**, afforded a 1:1 mixture of allylic alcohols which were converted to primary alcohols **(144)** and **(145)**. After separation by chromatography, **(144)** and **(145)** were transformed into (+)-6-epi- and (-)-1,6-diepicastanospermine respectively (overall yields from **(142)**: 6-epicastanospermine, 9%; 1,6-diepicastanospermine, 5.8%). The enantiomers of these two indolizidine tetrols, L-6-epi- and L-1,6-diepicastanospermine were also synthesized from D-gulonolactone,[68a,b] *via* lactam **(146)** using an identical sequence of reactions (Scheme 35).


(i) Swern oxidation
(ii) PhCH2ONH2.HCl
(iii) H2 / Pd-C / Boc2O
(147)
(148)
EtOC=CH2
OLi
(149)
(149)
PtO2 / H2
NaBH4
(150) (+(151) 7:2)
(151) (+(150) 3:1)
(i) HCO2H
(ii) Dowex 1x2 (OH-)
(iii) LiAlH4
(152)
(i) TFA aq
(ii) H2 / Pt-C
Castanospermine
1-Epicastanospermine

Scheme 36

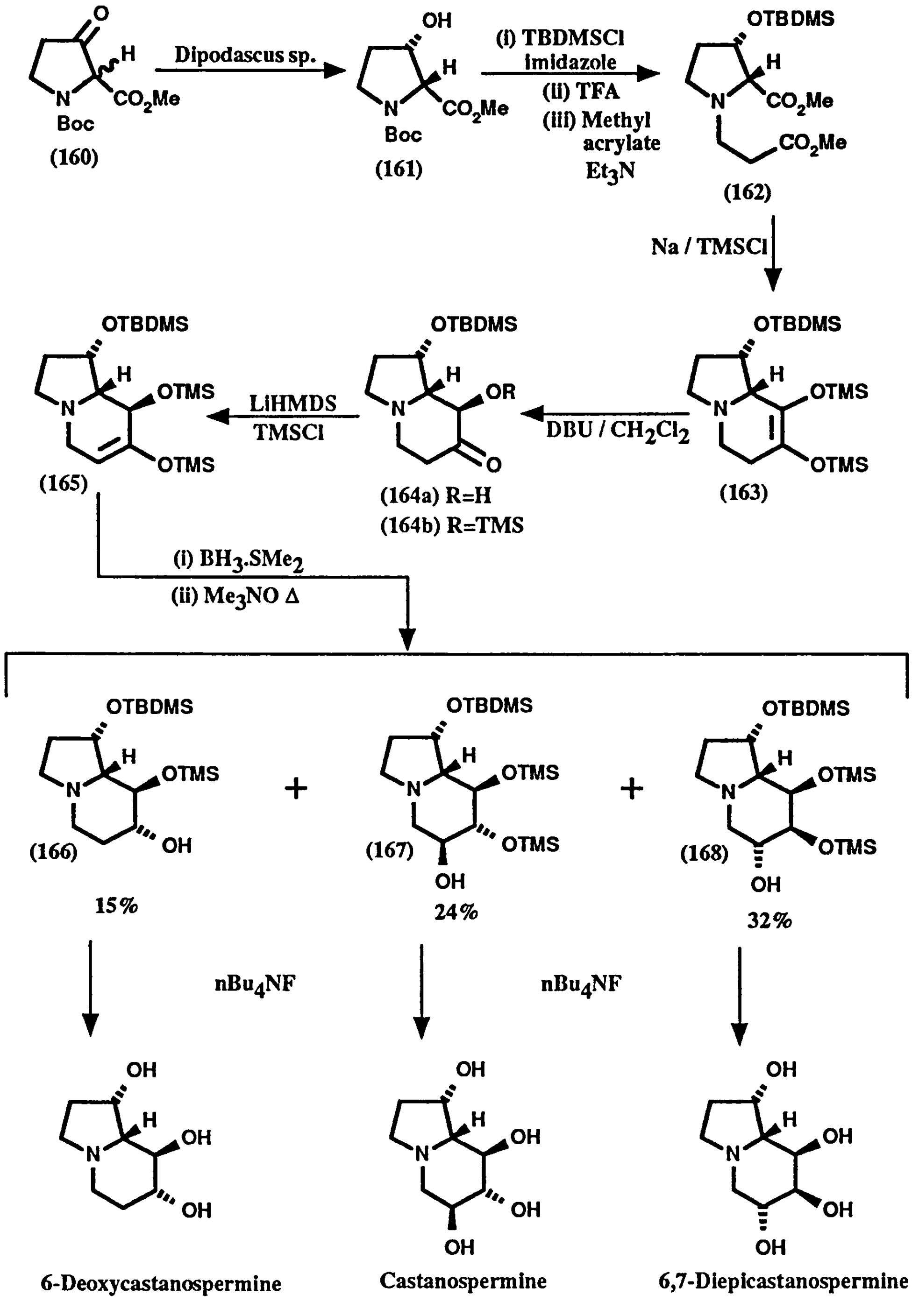
A lactone precursor has also been employed by a Merrell Dow group in a recent efficient synthesis of castanospermine[69] (Scheme 36). Reductive amination of the readily available glucuronolactone **(147)**[70] provided carbamate **(148)**[71] which was homologated to give hemiketal **(149)**. Reduction of **(149)** *via* catalytic hydrogenation afforded diol **(150)** as the major product (7:2 separable mixture of diastereoisomers), whereas borohydride reduction of **(149)** gave rise to diol **(151)** as the major product (3:1 separable mixture of diastereoisomers). Pyrrolidine **(152)** was obtained in three steps from **(150)** and deprotection of **(152)** followed by an intramolecular reductive amination reaction yielded (+)-castanospermine (17% overall yield from **(147)**). Identical transformations were applied to diol **(151)** to provide (-)-1-epicastanospermine (11% overall yield from **(147)**).


(i) BnOTMS
TMSOTf
Br2
(153)
(154)
(155)
(i) mCPBA
NaHCO3
SOCl2
MeOH
(+anomer)
(i) DIBAL
(ii) MsCl
Et3N
(156)
(i) NH3 aq
(ii) ClCH2COCl
(iii) Ac2O / cH2SO4
(157)
(i) (EtO)3P
(ii) K2CO3
(iii) Ac2O / py
DMAP
(158)
(i) Br2 / AcOH
Ac2O
AgOAc
(i) SOCl2
MeOH
(ii) Basic resin
(159)
(i) H2O
(ii) Ac2O / py
DMAP
(i) BH3.SMe2
(ii) H2 / Pd-C
Castanospermine

Scheme 37

2.3.2 Syntheses from Non-carbohydrate Precursors

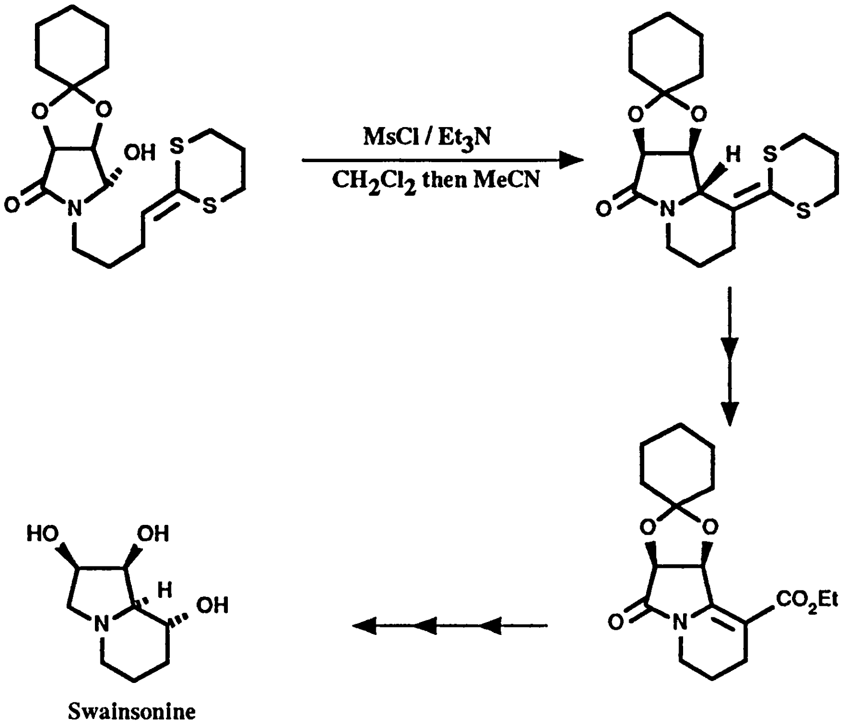
An unorthodox approach to the total synthesis of racemic castanospermine has been delineated by Vogel and Reymond.[72] Racemic 7-oxanorbornenone **(153)** was transformed into (±)-castanospermine in nineteen steps and 9.8% overall yield as depicted in Scheme 37. Bromination of ketal **(154)** provided the *O*-benzyl bromohydrin **(155)** *via* stereoselective migration of the *endo* *O*-benzyl group. Amination of mesylate **(156)**, prepared in four steps from **(155)**, afforded pyrrolidine **(157)** after *N*-acylation and transacetalization. Conversion of **(157)** into unsaturated lactam **(158)** was achieved *via* an intramolecular Wadsworth-Horner-Emmons reaction of the type previously employed by Fleet in the synthesis of 8-episwainsonine (see Scheme 21). Acetoxy-bromination of **(158)** provided a mixture of regioisomeric products which were converted to epoxide **(159)**. The synthesis of (±)-castanospermine was completed by hydrolysis of **(159)** followed by reduction and *O*-deprotection. Since both enantiomers of the starting material **(153)** are available in optically pure form,[72] the methodology could be used to prepare either enantiomer of castanospermine. Furthermore, some of the intermediates prepared in this synthesis may find value as precursors to stereoisomers and analogues of castanospermine.



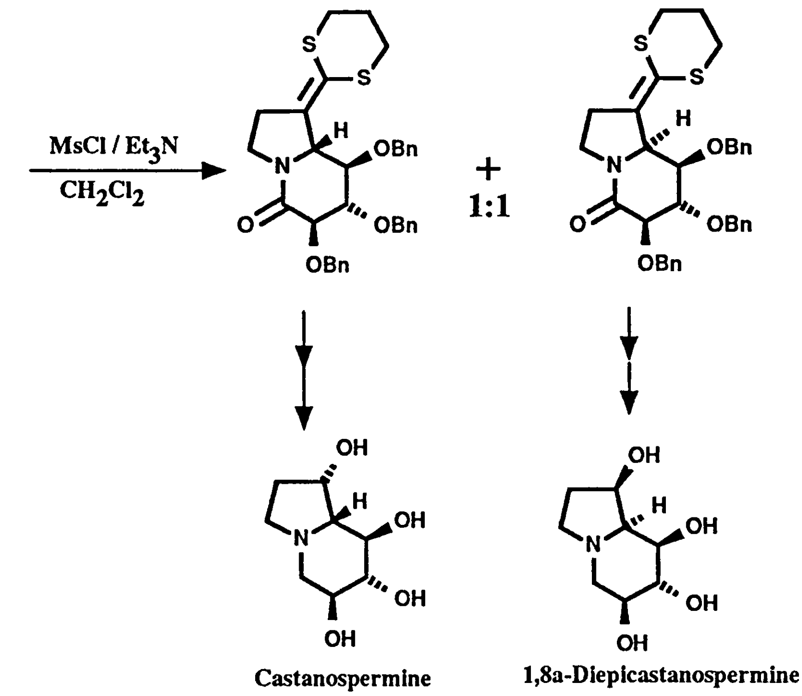
Dipodascus sp.
(i) TBDMSCl imidazole
(ii) TFA
(iii) Methyl acrylate Et_3N
Na / TMSCl
DBU / CH_2Cl_2
LiHMDS TMSCl
(i) $BH_3.SMe_2$
(ii) Me_3NO Δ
(160)
(161)
(162)
(163)
(164a) R=H
(164b) R=TMS
(165)
(166)
(167)
(168)
15%
24%
32%
nBu_4NF
6-Deoxycastanospermine
Castanospermine
6,7-Diepicastanospermine

Scheme 38

The utility of biocatalytic methodology has been demonstrated by Sih's group in a total synthesis of castanospermine.[73] Chiral building-block **(161)** was obtained in enantiomerically pure form from the yeast reduction of the known β-keto ester **(160)** (Scheme 38). After the straightforward conversion of **(161)** to diester **(162)**, the latter was subjected to acyloin condensation to give the bicyclic amine **(163)**. Interestingly, the conversion of **(163)** to a mixture of amino ketones **(164a)** and **(164b)** could be accomplished by treatment with DBU in dichloromethane. Hydroboration of silyl enol ether **(165)**, prepared from either **(164a)** or **(164b)**, followed by oxidation afforded a mixture of **(166)**, **(167)** and **(168)** which were desilylated to give (+)-6-deoxycastanospermine, (+)-castanospermine and (+)-6,7-diepicastanospermine respectively. The overall yield of key intermediate **(165)** was 43% and the authors are currently investigating the diastereoselectivity of the hydroboration reaction.

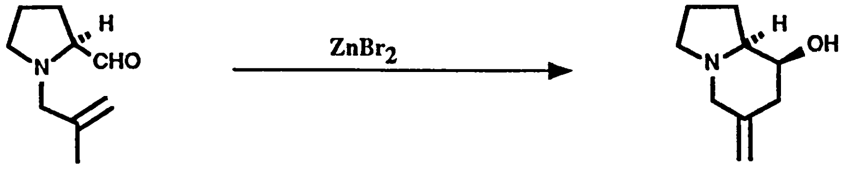


Scheme 39

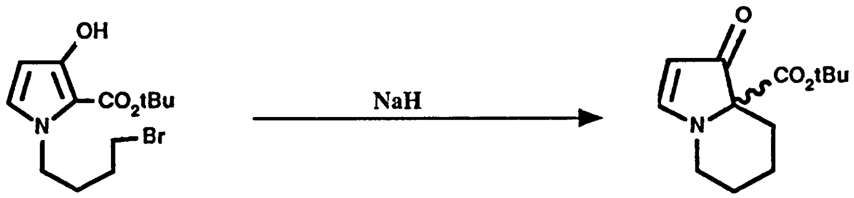


Scheme 40

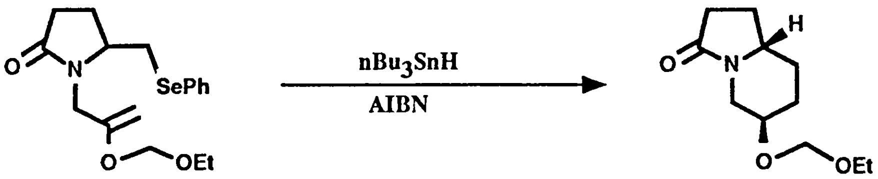
During the compilation of this review, Chamberlin and Miller have reported the synthesis of (-)-swainsonine, (+)-castanospermine and (+)-1,8a-diepicastanospermine using cationic cyclizations induced by acyliminium ions as a key step[74] (Schemes 39 and 40). The required hydroxy lactam intermediates were prepared from monosaccharide lactones.



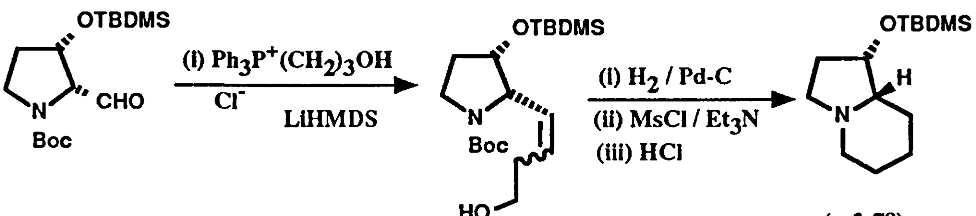
(ref. 75)



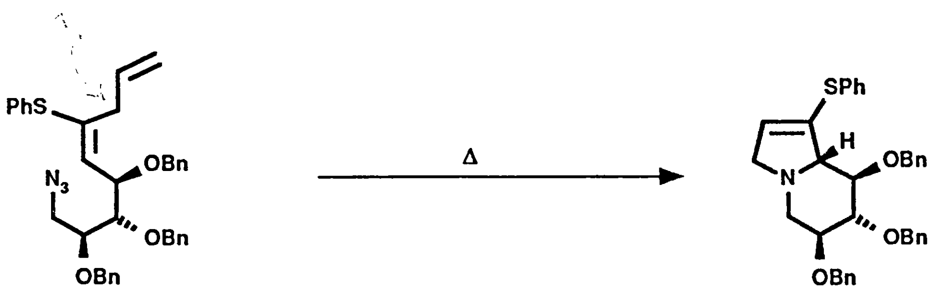
(ref. 76)



(ref. 77)



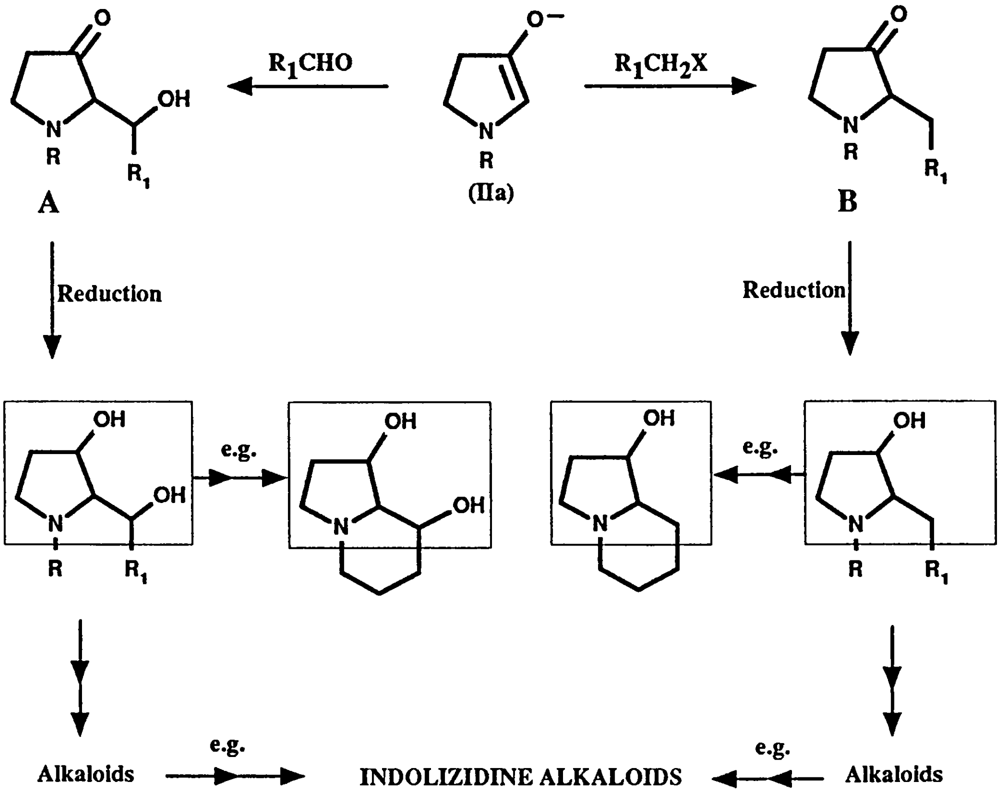
(ref. 78)



(ref. 79)

Scheme 41

Finally, a number of recent methods have been developed for the synthesis of the indolizidine skeleton which may enjoy future application to the preparation of hydroxylated derivatives (Scheme 41).


R1CHO
R1CH2X
(IIa)
A
B
Reduction
Reduction
e.g.
e.g.
Alkaloids
e.g.
INDOLIZIDINE ALKALOIDS
e.g.
Alkaloids

Scheme 42

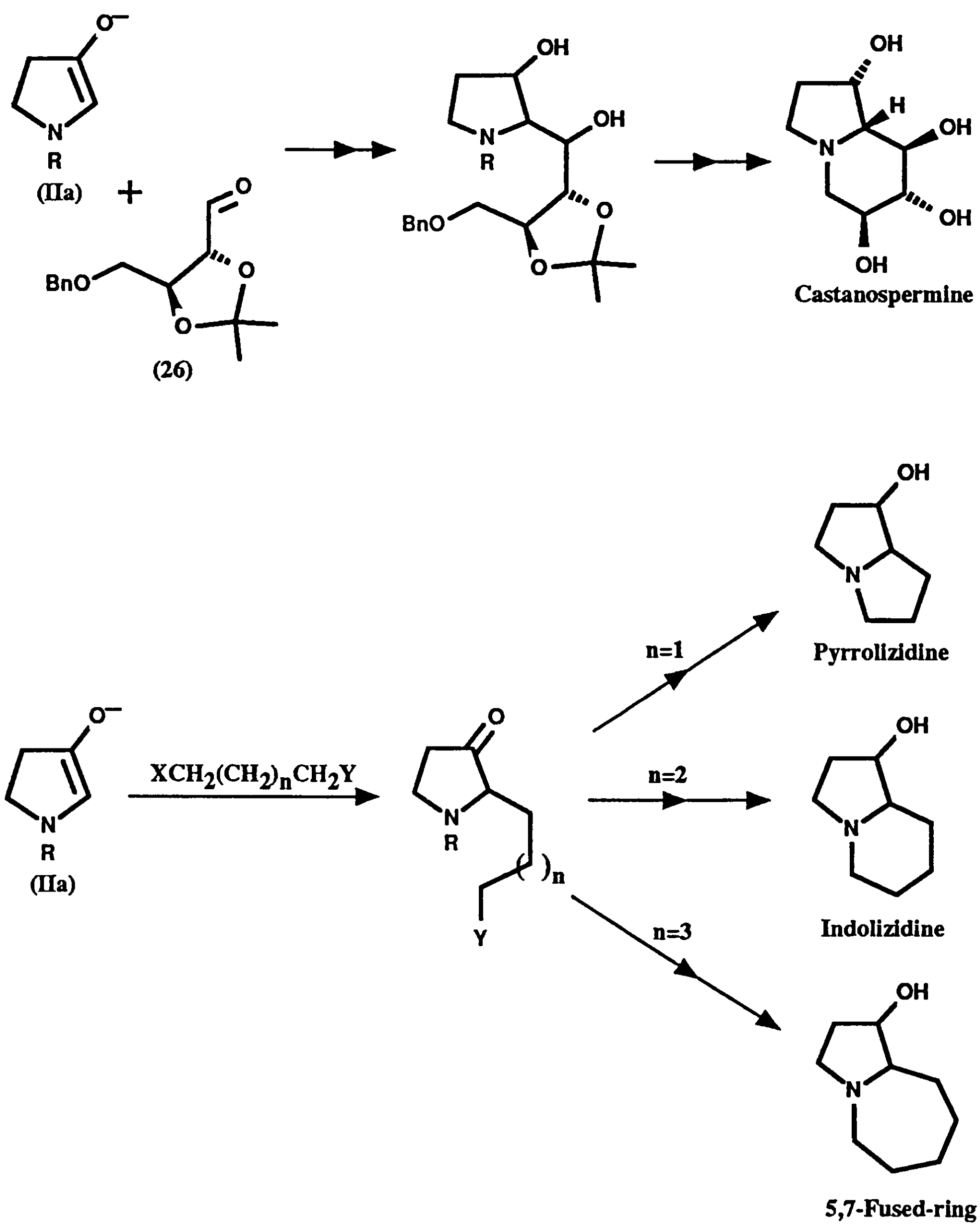
3 3-Pyrrolidinones as Potential Synthons for Indolizidines

3.1 General Synthetic Approach

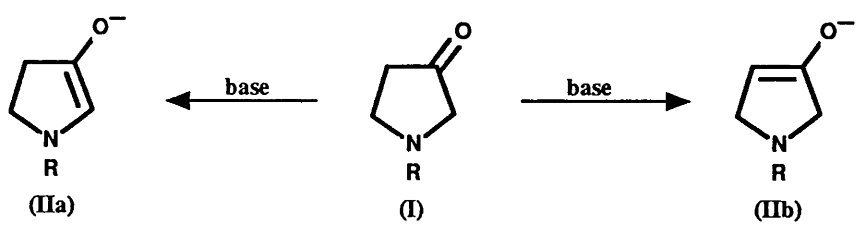
Most of the chemical syntheses of polyhydroxylated indolizidines outlined in the previous section utilize monosaccharides as starting materials. Whilst these carbohydrate-based precursors are extremely useful for the enantioselective synthesis of indolizidines with unambiguous absolute stereochemistry, the syntheses involved are limited in terms of flexibility for the introduction of structural modifications. Because of the need for novel analogues and stereoisomers of biologically active, polyhydroxylated indolizidines (see Section 1.7), there is increasing interest in the development of alternative synthetic approaches to such molecules.

Our own approach to the synthesis of hydroxylated indolizidines originates from a general interest in the chemistry of heterocyclic ketones. In particular, we were interested in the potential synthetic applications of a 3-pyrrolidinone enolate (**IIa**) as a nucleophilic unit for the construction of alkaloid precursors (Scheme 42). We envisaged that enolate (**IIa**) could be employed in either an aldol reaction or an alkylation to provide 2-substituted-3-pyrrolidinones **A** or **B** respectively, and that these molecules could function as key intermediates in the synthesis of alkaloids containing a 2-substituted-3-hydroxypyrrolidine subunit in general.[1b,80]

Clearly, this approach is particularly appropriate for the synthesis of polyhydroxylated indolizidines. The proposed strategy would not only be highly convergent, but also inherently flexible, since the desired pattern of substitution and stereochemistry at hydroxyl-bearing centres in the newly-formed ring of the product might be embodied in the electrophile chosen



Scheme 43



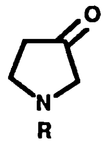
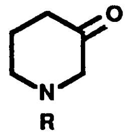
Scheme 44

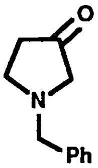
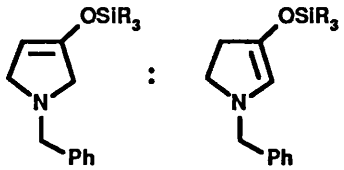
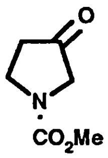
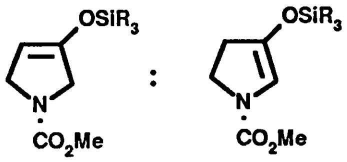
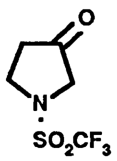
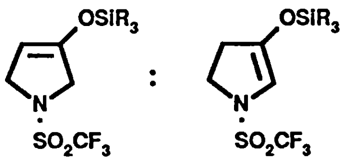
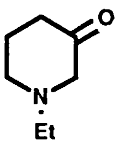
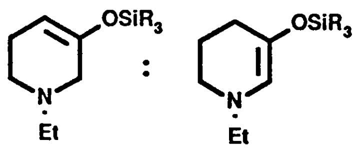
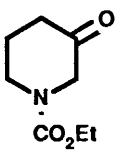
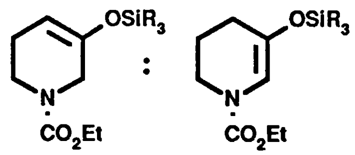
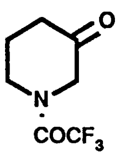
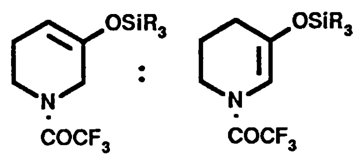
for reaction with the enolate. Thus, chiral aldehyde **(26)**[138,139] (see Results and Discussion, Schemes 17 and 55) emerges as a candidate for aldol reaction with **(IIa)** in the projected synthesis of castanospermine (Scheme 43).

The wide range of suitable electrophiles that are available would allow a diverse range of fused bicyclic natural products to be targeted and these need not be limited to indolizidines. Use of a three-carbon electrophile would give a precursor to the pyrrolizidine alkaloids,[81] whereas five-carbon electrophiles could be employed to afford precursors of alkaloids containing the 5,7-fused ring system[82] (Scheme 43).

For the reasons outlined in Section 1.7, the ultimate aim of the work described in this thesis was to develop a synthesis of hydroxylated indolizidine alkaloids and therefore castanospermine was chosen as a synthetic target. However, the success of the proposed synthetic approach relies upon the ready availability of enolate **(IIa)** and herein lies a problem. Deprotonation of the 3-pyrrolidinone **(I)** gives rise to mixtures of C-2 and C-4 enolates **(IIa)** and **(IIb)** respectively, and the level of regiocontrol that can be exercised in this enolization step dramatically limits the synthetic utility of such enolates (Scheme 44). The regioselective deprotonation of unsymmetrically substituted ketones is a general problem associated with enolate formation[83] but there are special considerations that apply to the enolization of heterocyclic ketones. Relatively little work has been done in this area. One particularly pertinent report includes data for the enolization tendencies of 3-pyrrolidinones and 3-piperidinones.[84a] These results are outlined in the next section and this is followed by a discussion of the factors which may affect the regiochemistry of enolate formation in these and related systems.

Table 1 : Enolization of 3-Pyrrolidinones and 3-Piperidinones :

 and 

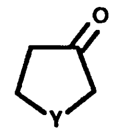
Ketone	Product Ratio	Method A[a]	Method B[b]	Method C[c]
		1:0.43	1:0.05	dec.[d]
		1:1	1:0.6	NE[e]
		1:0.33	dec.[d]	NE[e]
		1:0.2	1:0.02	1:6
		1:3.5	1:3	1:19
		1:4	1:49	NE[e]

[a]Method A : Ketone + LDA (1.1-1.5eq) / THF -78°C 30min then chlorotrialkylsilane
[b]Method B : Ketone + LiHMDS (0.8 eq) / THF -78°C 30min then 0°C 30min then chlorotrialkylsilane
[c]Method C : Ketone + chlorotrialkylsilane (1.2eq) + triethylamine (2.4eq) / DMF / 80°C / 48h
[d]Decomposition
[e]Not Examined

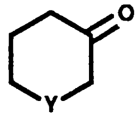
3.2 *The Enolization of 3-Pyrrolidinones and 3-Piperidinones*

In the study of the regioselective enolization of a number of α-amino ketones, Garst and coworkers showed that, in general, the preferred mode of enolization of *N*-substituted-3-pyrrolidinones is away from the nitrogen atom leading to a predominance of C-4 enolates **(IIb)**[84] (Scheme 44).

The data obtained by these workers for the enolization of 3-pyrrolidinones and 3-piperidinones is shown in Table 1. Of the three methods of enolization detailed, methods A and B involve the generation of enolates which are subsequently trapped with chlorotrialkylsilanes to give silyl enol ethers. The assumption was made that the observed ratios of silyl enol ethers reflect the relative proportions of C-2 and C-4 enolates present prior to trapping. If this is true, then it can be seen that the desired 3-pyrrolidinone C-2 enolate is available at best as a 1:1 mixture with the C-4 enolate (R = CO_2Me, Method A). In general, *N*-substituted 3-pyrrolidinones show a marked tendency to enolize away from the nitrogen atom. Indeed, high levels of regiocontrol can be exercised in formation of the C-4 enolate (e.g. R = benzyl, Method B). In contrast, the 3-piperidinones exhibit a preference for enolization towards the nitrogen atom, especially when an electron-withdrawing group is attached, and excellent selectivity may be achieved in generation of the six-membered C-2 enolate (e.g. R = trifluoroacetyl, Method B).



(III)



(IV)

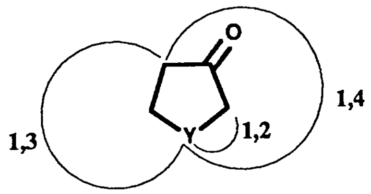
a Y = O
b Y = S
c Y = NR

Fig. 5

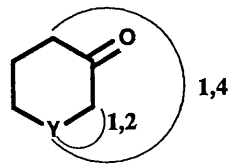
3.3 *Factors Affecting the Regiochemistry of Enolate Formation*

There are a number of factors which may affect the regiochemistry of enolization in these systems, which form part of a general class of heterocyclic ketones ((III) and (IV), Fig. 5)

For the nitrogen-containing systems it is likely that the mode of enolization is subject to influence by the nitrogen substituent and that this additional variable will complicate the picture. The kinetic acidity of the C-2 protons in these systems might be expected to increase when an electron-withdrawing group is attached to the nitrogen atom. Whilst the ratio of C2:C4 enolate is highest for both *N*-benzyl-3-pyrrolidinone and *N*-ethyl-3-piperidinone when kinetic base-mediated conditions are employed (compare ratios obtained using Method A with those obtained using Method B), enolization away from the nitrogen atom still predominates. However, when an ethoxycarbonyl group is attached to nitrogen, the ratio of C2:C4 enolate for 3-piperidinones switches to 3.5:1 and this improves to 4:1 when a trifluoroacetyl group is used. An improvement in the C2:C4 enolate ratio is also observed for the 3-pyrrolidinone series when the *N*-benzyl group is replaced by a methoxycarbonyl group. In contrast, when a triflate group is employed as nitrogen substituent the proportion of C-2 enolate formed <u>decreases</u> compared to the proportion observed for the *N*-benzyl derivative. At first sight this seems somewhat puzzling. It appears that electron-withdrawing nitrogen substituents do not affect the kinetic acidity of the C-2 protons in 3-pyrrolidinones to the same extent that they do in the 3-piperidinone series. However, the situation is complicated by the fact that 3-pyrrolidinones are not only α-amino ketones but also β-amino ketones and the electronic nature of the nitrogen substituent might be expected to affect the C-4 protons as well as the C-2 protons. β-Amino substitution in acyclic ketones bearing α-protons in



(III)



(IV)

a Y = O
b Y = S
c Y = NR

Fig. 6

similar steric environments has been shown to exert a kinetic acidifying effect on the α-protons proximal to the β-substituent[85]. The C-4 protons may also experience an additional level of activation. The corresponding C-4 protons of the five-membered sulphur analogue, **(IIIb)** (Fig. 5) have been shown to exhibit unexpectedly high kinetic acidity relative to the C-2 protons.[86] A "1,4 effect" of unknown origin was invoked to account for this phenomenon, whereby the C-4 protons are activated by the heteroatom Y through the methylene-carbonyl-methylene array. Similar effects have been observed in acyclic systems.[87]

Thus, in five-membered heterocyclic ketones **(III)**, the direction of enolization under kinetic control will depend upon the relative contributions from the 1,2-, 1,3- and 1,4-effects in operation, whilst in six-membered systems **(IV)**, contributions from 1,2- and 1,4-effects must be considered (Fig. 6). Moreover, the 1,2-effect should not be viewed solely in terms of the potential inductive kinetic acidifying capability of Y. [84a, 94a,b] Deprotonation at C-2 could lead to severe repulsions between the lone-pair of the conformationally restrained heteroatom and the enolate anion. This phenomenon could affect both the kinetic acidity of the C-2 protons and the thermodynamic stability of the resulting enolate.[88b] Hine *et al* concluded that the rate of enolate formation is decreased by such interactions.[88] This stereoelectronic effect has been implicated in the observed tendency of tetrahydropyranone **(IVa)** and its derivatives to undergo preferential enolization away from the oxygen atom.[89,90] The effect does not appear to be important, however, with sulphur as the heteroatom. 3-Thiacyclohexanone **(IVb)** undergoes enolization towards the sulphur atom under both kinetic and thermodynamic conditions,[89] and acetylation of the enolate derived from **(IIIb)** results in 85% substitution at C-2 and only 15% substitution at C-4[91], although it is not clear whether thermodynamic or kinetic control is operating in this case. Little information is

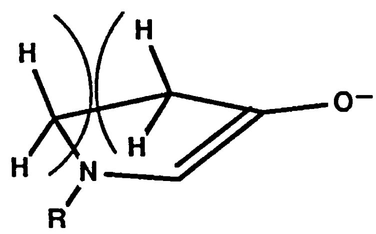


Fig. 7

available on the enolization tendencies of dihydrofuranone (**IIIa**) although low yields of C-2 aldolization have been reported as well as C-2,C-4-bis aldolization.[92]

In ketonic systems lacking a conformational constraint, bond rotation may allow an α-heteroatom to orient its lone pair of electrons such that enolization towards the heteroatom may occur without giving rise to an unfavourable electronic arrangement.[93] In these cases, enolization towards the heteroatom is often observed.[94]

With 3-pyrrolidinones (**IIIc**) and 3-piperidinones (**IVc**) the situation is again complicated by the electronic nature of the nitrogen substituent, this time with respect to its ability to delocalize the nitrogen lone pair, which is not necessarily a function of its inductive electron-withdrawing aptitude. If the nitrogen substituent is capable of delocalizing the nitrogen lone pair of electrons, then any unfavourable lone pair-enolate anion interaction should be diminished, and a higher proportion of the respective C-2 enolates might be expected to result. This postulate is in accordance with the general trends apparent from Garst's experimental findings. Another characteristic of the nitrogen substitutent which should not be discounted is its steric bulk, which may also adversely affect the kinetic acidity of the C-2 protons.

The enolization of 3-pyrrolidinones may also be influenced by a conformational effect. In all cases where C-2 enolization occurs the five-membered ring becomes somewhat flattened and the two remaining methylenes become eclipsed (Fig. 7). The extent to which this effect contributes to the thermodynamic destabilization of the C-2 enolates is unclear. However, such eclipsing interactions do not arise in either enolate of the corresponding six-membered system where good C-2 enolate selectivities are

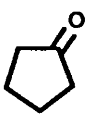
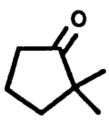
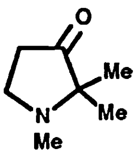
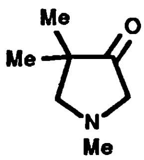
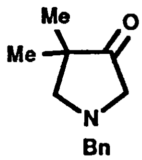
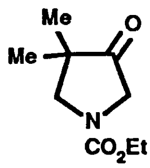
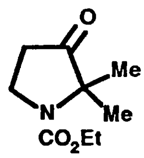
Ketone :						
	(V)	**(VI)**	**(VII)**	**(VIII)**	**(IX)**	**(X)**
pK_a :	**25.8**	**26.2**	**24.8**	**27.7**	**26.4**	**22.0**

Table 2



(XI)

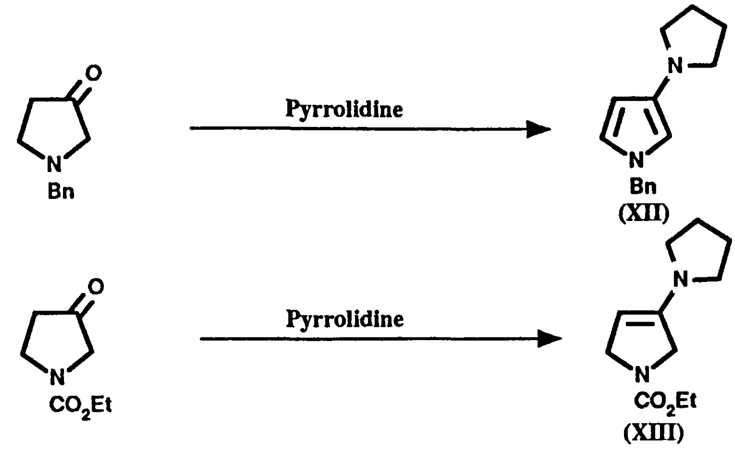
observed (see also Sections 3.5 and 3.6 below).

3.4 pKa Data for Related 3-Pyrrolidinones

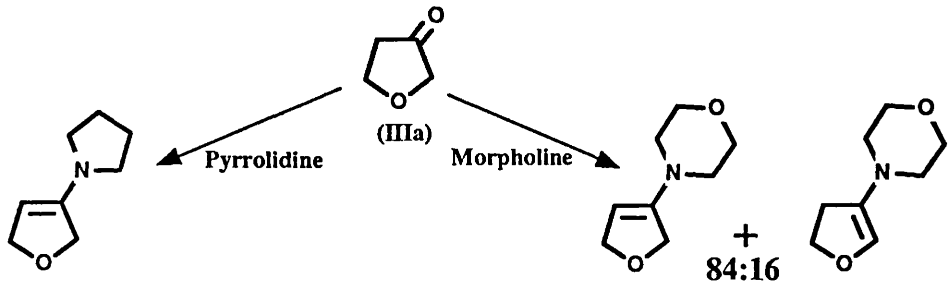
It is pertinent here to include pKa data for some related ketocyclic systems measured by Professor F.G. Bordwell's group as part of a collaborative study[95] (Table 2). As expected, the pKa of *N*-substituted-4,4-dimethyl-3-pyrrolidinones decreases with increasing electron-withdrawing/lone pair-delocalizing character of the nitrogen substituent. The measurement of pKa for **(VII)** was hampered by the propensity of the anion to undergo β-elimination and this also applied to carbamate **(XI)** for which a pKa measurement could not be made. Although care must be exercised in attempting to correlate data for these gem-dimethyl substituted derivatives with Garst's experimental observations, it is interesting to note the relatively large difference in pKa between **(VII)** and **(VIII)**, which is in accordance with the enolization tendencies of *N*-alkyl-3-pyrrolidinones under equilibrating conditions (see Table 1). It is not unreasonable to assume that the equilibrium acidities of the amino ketones in Table 2 will be dependent on some of the factors discussed in the previous section.

3.5 Factors affecting the Regiochemistry of Acid-Catalyzed Enolization and of Enamine Formation

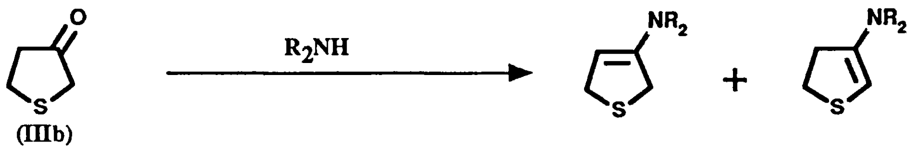
The "thermodynamic acid" conditions employed by Garst for the enolization of these cyclic amino ketones do not involve enolates and therefore the observed ratios of silyl enol ethers which are formed do not necessarily reflect the corresponding enolate ground state stabilities. Under these conditions the relative stabilities of enamine/allylamine pairs may become relevant for the *N*-alkyl derivatives. The reversal of the selectivity observed for



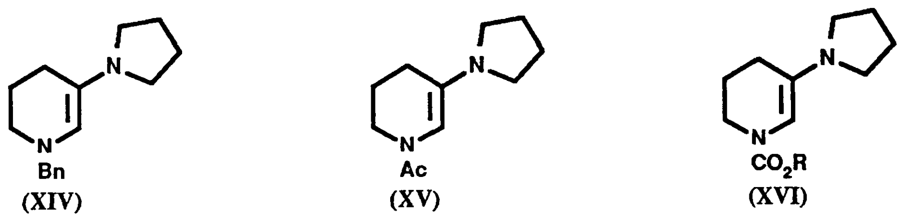
Scheme 45



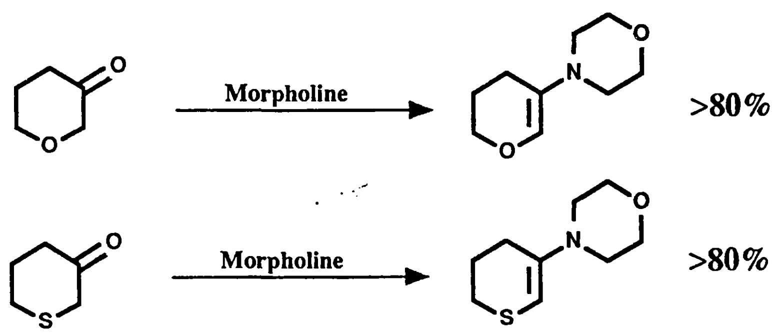
Scheme 46



Scheme 47

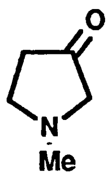


Scheme 48

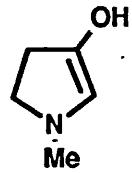


Scheme 49

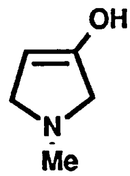
the enolization of *N*-ethyl-3-piperidinone is in accordance with the apparent greater thermodynamic stability of enamines relative to allylamines in six-membered systems.[(96)] Enolization of *N*-benzyl-3-pyrrolidinone under these conditions led to decomposition. Joule has concluded that, in contrast to the six-membered system, $\Delta^{3,4}$ pyrrolines are thermodynamically more stable than the $\Delta^{2,3}$ isomers[(97)] which, despite their potential synthetic utility[(98)], are notoriously unstable.[(99)] Again, eclipsing interactions between vicinal hydrogens may contribute to this instability and may also explain the observed regiochemical preferences in enamine formation from five-membered heterocyclic ketones in general. For example, although attempts to prepare the pyrrolidine enamine of *N*-benzyl-3-pyrrolidinone resulted in formation of pyrrole **(XII)** *via* an oxidation process,[(100)] the reaction of *N*-ethoxycarbonyl-3-pyrrolidinone with pyrrolidine yielded the 2,5-dihydropyrole **(XIII)**, a $\Delta^{3,4}$ pyrroline[(101)] (Scheme 45). Similarly, dihydrofuranone **(IIIa)** gives a 2,5-dihydrofuran with pyrrolidine[(102)] and a mixture of 2,5-dihydro- and 4,5-dihydrofurans in a ratio of 84:16, with morpholine[(103)] (Scheme 46). Dihydrothiophenone **(IIIb)** gives mixtures of isomeric enamines with a number of secondary amines[(104)] (Scheme 47). In contrast, the formation of enamines from six-membered heterocyclic ketones occurs with the opposite regioselectivity. Thus, the pyrrolidine enamines **(XIV)-(XVI)** of *N*-benzyl-[(105)], *N*-acetyl-[(106)] and *N*-alkoxycarbonyl-3-piperidinone[(107)] are the exclusive products (Scheme 48). Similarly, enamine formation from **(IVa)**[(89,108)] and **(IVb)**[(89)] produced that regioisomer with the double bond toward the heteroatom in greater than 80% yield (Scheme 49). These results parallel the observed selectivities for enol ether formation from 3-piperidinones under Garst's "thermodynamic acid" conditions.



(XVII)

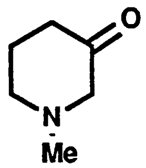


(XVIIa)

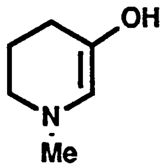


(XVIIb)

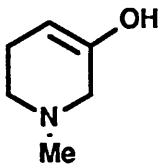
Fig. 8



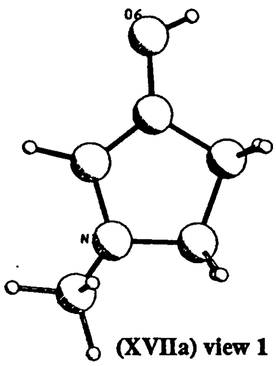
(XVIII)



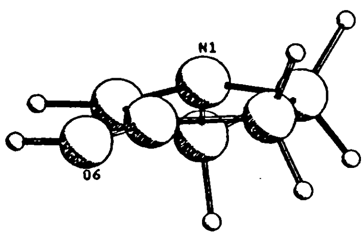
(XVIIIa)



(XVIIIb)

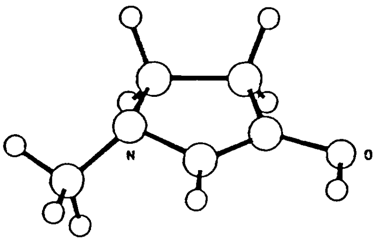


(XVIIa) view 1

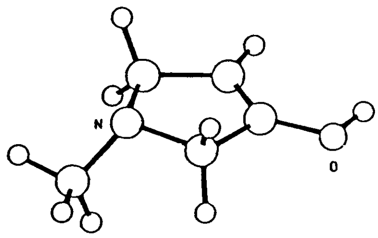


(XVIIa) view 2

Fig. 9



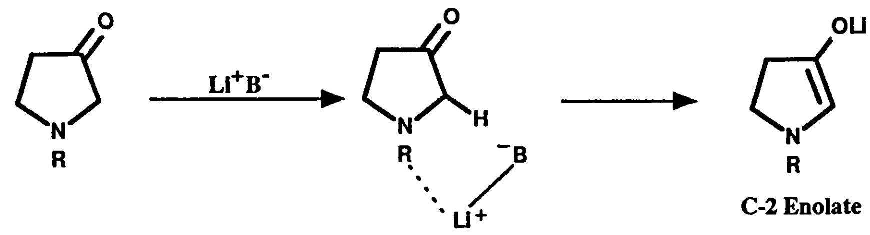
(XVIIa) view 3



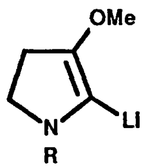
(XVIIb)

3.6 *Supplementary* Ab Initio *Energy Calculations*

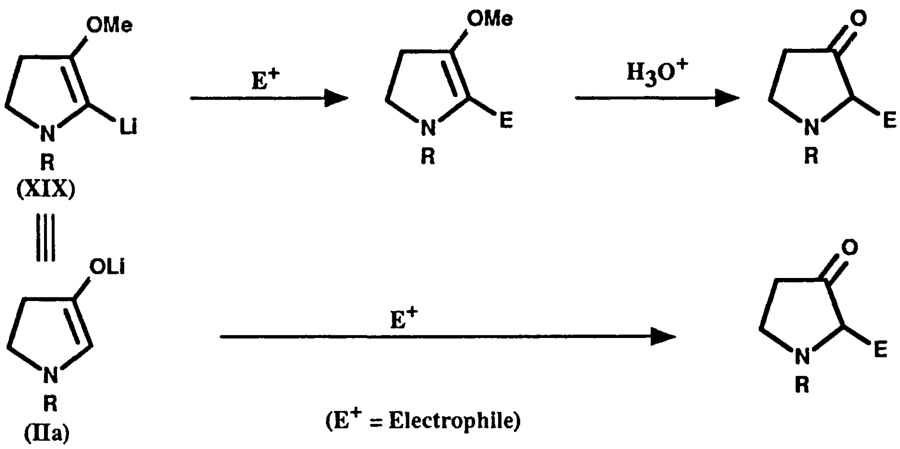
As a supplement to Garst's experimental data, we believed it would be instructive to perform some energy calculations relating to these enolization processes. Relative energies of the two possible enols available from 3-pyrrolidinone **(XVII)** and 3-piperidinone **(XVIII)** (Fig.8) were determined from *ab initio* calculations undertaken at SmithKline Beecham Research, Harlow by Dr. G Stemp.[200] For the 3-pyrrolidinones, enol **(XVIIb)** was calculated to be 1.6 Kcalmol^{-1} lower in energy than enol **(XVIIa)**. This corresponds to a 95:5 ratio of **(XVIIb)** : **(XVIIa)** assuming a Boltzmann distribution at 0°C and agrees almost exactly with Garst's experimental findings for enolization under base mediated equilibrating conditions (Method B, *N*-benzyl, 1:0.05, C-4:C-2 enolate). Furthermore, the eclipsing interaction of the two methylenes in the energy-minimized conformation of enol **(XVIIa)** is shown very clearly (views 1-3; Fig. 9). For the piperidinones the situation is slightly complicated as the Cambridge Crystallographic Data Base shows that for related $\Delta^{2,3}$ tetrahydropyridines only one conformation (*N*-methyl equatorial) is found whereas for $\Delta^{3,4}$ tetrahydropyridines two conformations (*N*-methyl equatorial and *N*-methyl axial) are found. Both conformations were used as the starting structures for energy-minimization procedures. If the conformation with the *N*-methyl group equatorial is used, then enol **(XVIIIa)** is 2.2 Kcalmol^{-1} lower in energy than enol **(XVIIIb)**. If the conformation with the *N*-methyl group axial is used, then enol **(XVIIIa)** is 1.75 Kcalmol^{-1} lower in energy than enol **(XVIIIb)**. These values correspond to ratios of **(XVIIIa)**:**(XVIIIb)** of 98:2 and 94:6 respectively. This result is not consistent with the experimentally observed ratio of silyl enol ethers obtained from *N*-ethyl-3-piperidinone under base mediated equilibrating conditions (Method B, 1:0.02, C-4:C-2 enolate). It is more in keeping with the experimental ratio observed for enolization under "thermodynamic acid" conditions (Method C,



Scheme 50



(XIX)



Scheme 51

1:6, C-4:C-2, silyl enol ether) a process in which enols have been suggested as possible intermediates.[84a]

Of course, the calculated relative energies of enols should not be regarded as an indication of the relative energies of the corresponding enolates, where factors such as charge distribution and cation coordination are involved. These calculations should be considered only in the broad context of the overall regiochemical preferences of what are clearly complex and subtle processes involving numerous structural and electronic variables. Within this context, the calculations suggest that 3-pyrrolidinones are markedly more reluctant to enolize towards the heteroatom than 3-piperidinones, and therefore complement the experimental findings of Garst.

3.7 Proposed Solutions

Our initial approach to the problem of poor selectivity in the enolization of 3-pyrrolidinones involved the use of a directing group attached to the nitrogen atom which might encourage deprotonation at C-2 *via* coordination with a lithium base (Scheme 50). This idea was based on the work of Beak and Meyers who have studied this type of process in detail and reported extensively on its successful application to the α-substitution of amines.[115-117,119,151] Our efforts in this area soon led to the discovery of a novel method for the preparation of metalated enol ethers of type **(XIX)** and we then perceived that organolithiums of this type could potentially function as synthetic equivalents of the required C-2 enolate **(IIa)** *via* reacton with an electrophile and subsequent hydrolysis of the resulting adducts to give the desired 2-substituted-3-pyrrolidinones (Scheme 51).

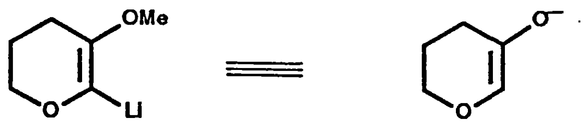


Fig. 10

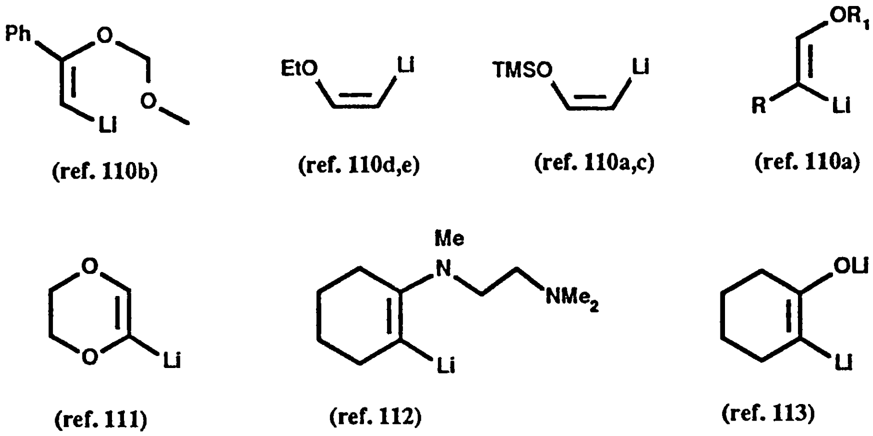
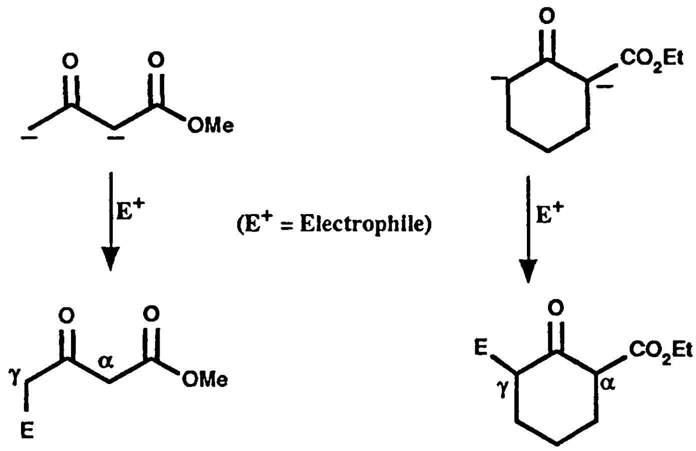
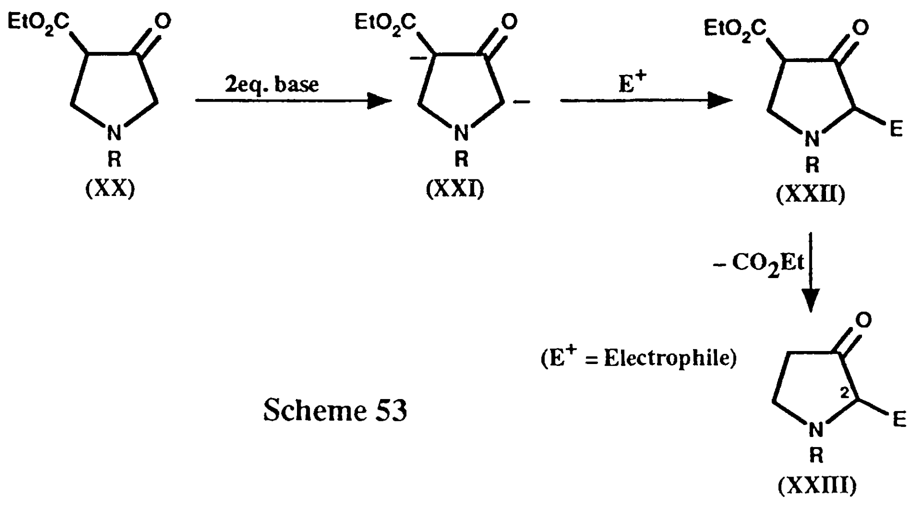


Fig. 11



Scheme 52



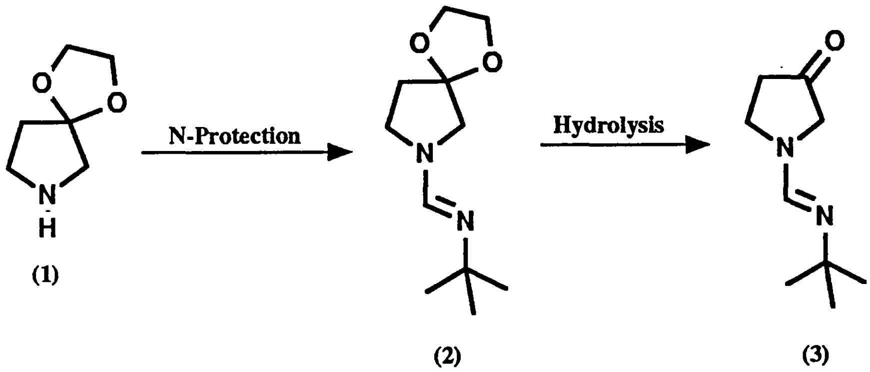
Scheme 53

Work in our own laboratory has previously established that a β-lithiated enol ether may be used as a chemical equivalent of the disfavoured enolate isomer of tetrahydropyran-3-ones[109] (Fig. 10). Other workers have demonstrated the use of acyclic[110] and cyclic[111] β-lithiated enol ethers as well as β-lithiated enamines[112] and α-keto dianions[113] as enolate equivalents (Fig. 11).

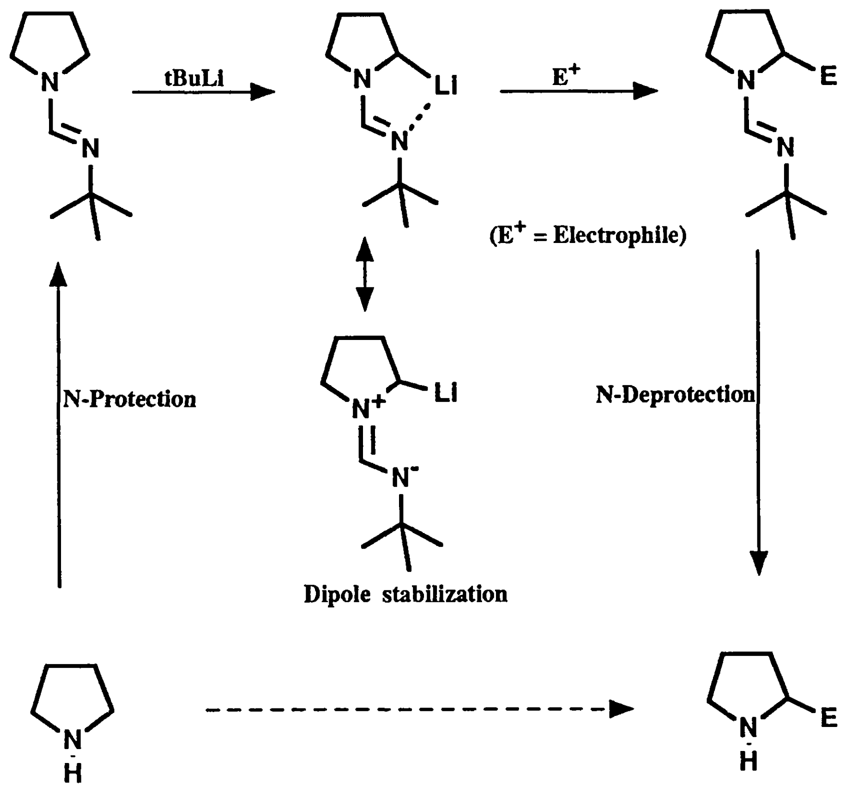
A second approach to the problem was also considered. It is well known that dianions of simple β-keto esters undergo reaction with electrophiles to give δ-subtituted products (Scheme 52).[172-176] By analogy, a heterocyclic dianion of type **(XXI)**, which might be available from double deprotonation of a β-keto ester **(XX)**, should furnish 2-substituted products **(XXII)** on reaction with electrophiles and a subsequent deethoxycarbonylation would then yield the desired 2-substituted-3-pyrrolidinones **(XXIII)** (Scheme 53).

The results of our studies on the generation of species such as **(XIX)** and **(XXI)**, and their use as regiospecific 3-pyrrolidinone equivalents is discussed in the next section.

RESULTS AND DISCUSSION



Scheme 1



Scheme 2

RESULTS AND DISCUSSION

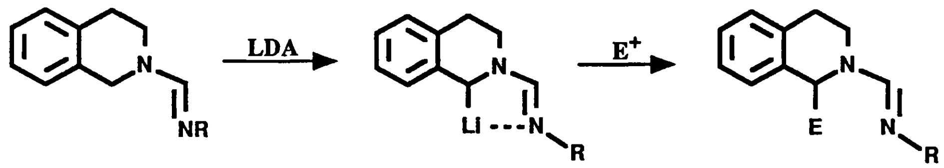
1 The Directed Lithiation of 3-Pyrrolidinone Derivatives

1.1 The Deprotonation of Formamidine Derivatives

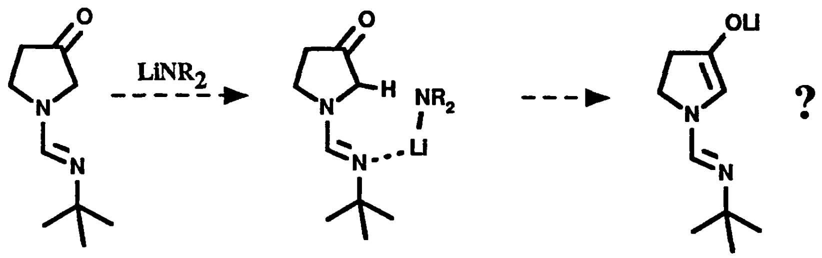
1.1.1 Initial Studies

The initial approach to the generation of a 3-pyrrolidinone C-2 enolate (see Introduction, Section 3.7) required the preparation of a 3-pyrrolidinone possessing a suitable nitrogen substituent. We envisaged that the 3-pyrrolidinone derivative **(3)**, with a formamidine moiety incorporating the ring nitrogen atom, would be a suitable substrate for the investigation of directed deprotonations, and that **(3)** might be prepared from the known amine **(1)**(114) *via* formamidine derivative **(2)** (Scheme 1).

The formamidine group was originally introduced by Meyers and coworkers as an activating group for the α-lithiation of amines(115g) and has proved extremely effective in facilitating deprotonation adjacent to the nitrogen atom of secondary amines.(115) The organolithium species generated in this way are stabilized both by intramolecular coordination of the heteroatoms with the lithium as well as by dipole-stabilization,(116) and subsequent alkylation provides access to α-substituted amines as illustrated in Scheme 2.(115a) Meyers and his associates have shown that this methodology is applicable to the synthesis of a range of nitrogen-containing molecules and the process has been extended to the preparation of optically active amines using chiral formamidine derivatives.(117) These workers have also provided compelling evidence for the formation of a complex between the formamidine moiety and the alkyllithium base, prior to deprotonation of the substrate.(118) The operation of such

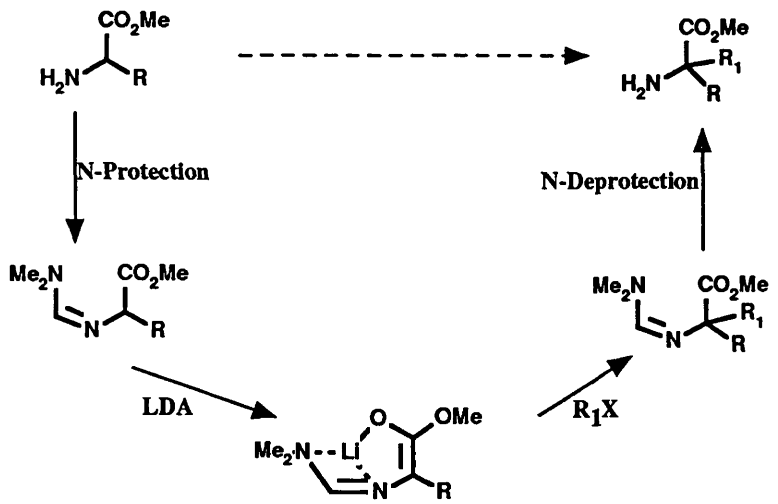


Scheme 3 (E^+ = Electrophile)



(3)

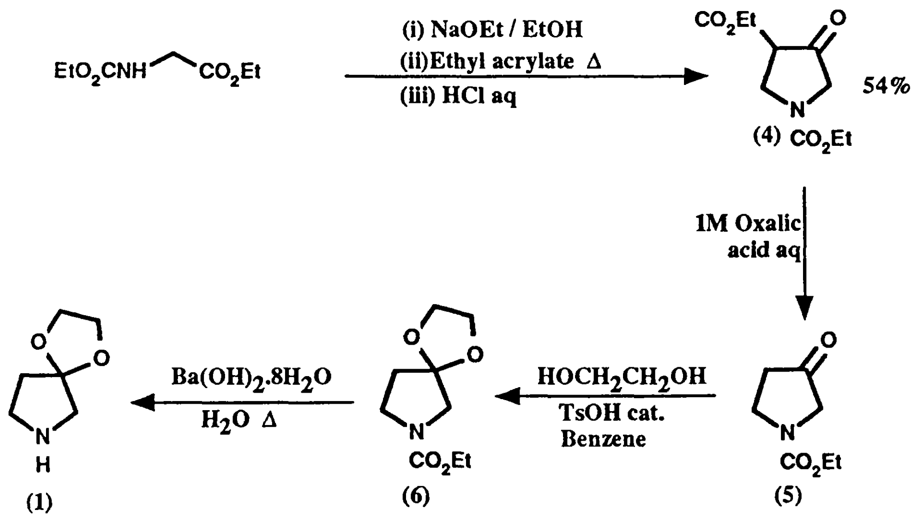
Scheme 4



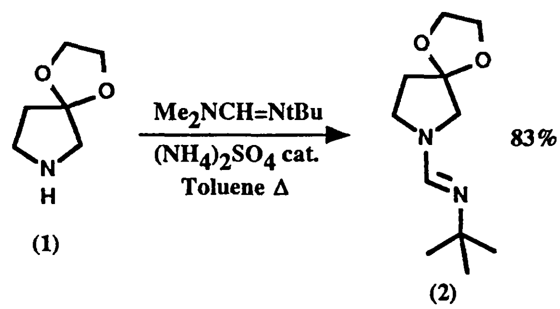
Scheme 5

"complex-induced proximity effects" can be important in controlling the course of ensuing transformations.[119]

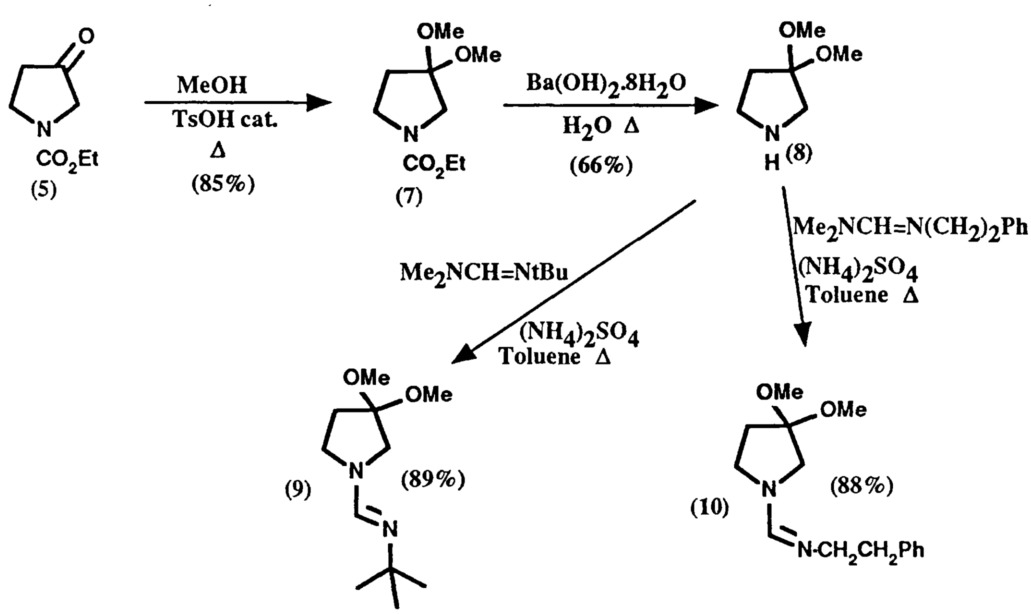
In the case of formamidine derivatives, systems possessing additional activation, such as tetrahydroisoquinoline derivatives, undergo deprotonation with LDA,[115e, 117h] although it is not clear if precomplexation occurs in these cases (Scheme 3). If the formamidine is indeed capable of complexation with lithium dialkylamide bases, then we might expect preferential deprotonation of (3) to occur at C-2 when treated with LDA, resulting in the formation of the desired C-2 enolate (Scheme 4). A related process has been described by Gschwend and Fitt for the α-alkylation of α-amino acids[120] (Scheme 5). In this case, the imino nitrogen atom of the formamidine moiety is derived from the primary amino group of the amino acid, so that the nitrogen atoms of the formamidine are transposed relative to the site of deprotonation/alkylation, compared to the nitrogen atoms of the formamidines derived from secondary amines, such as those depicted in Schemes 2 and 3. In general, the enolization of esters is not complicated by the regiochemical considerations which apply to the deprotonation of unsymmetrical ketones, such as 3-pyrrolidinones.



Scheme 6

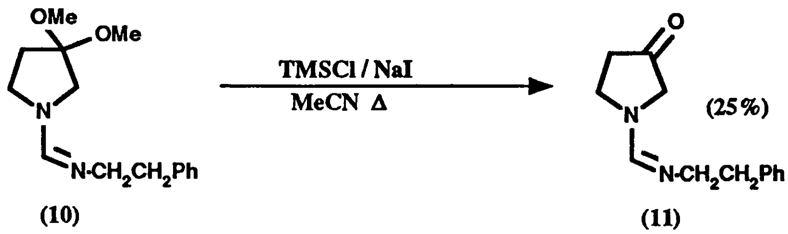


Scheme 7

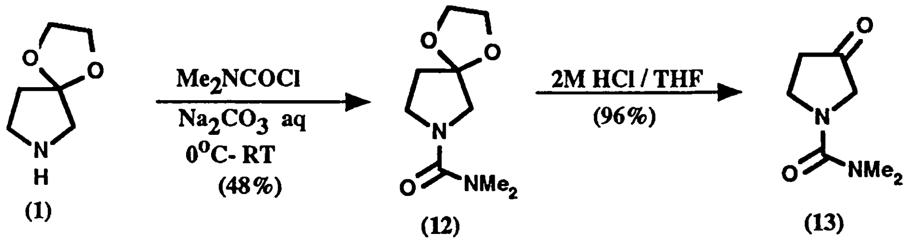


Scheme 8

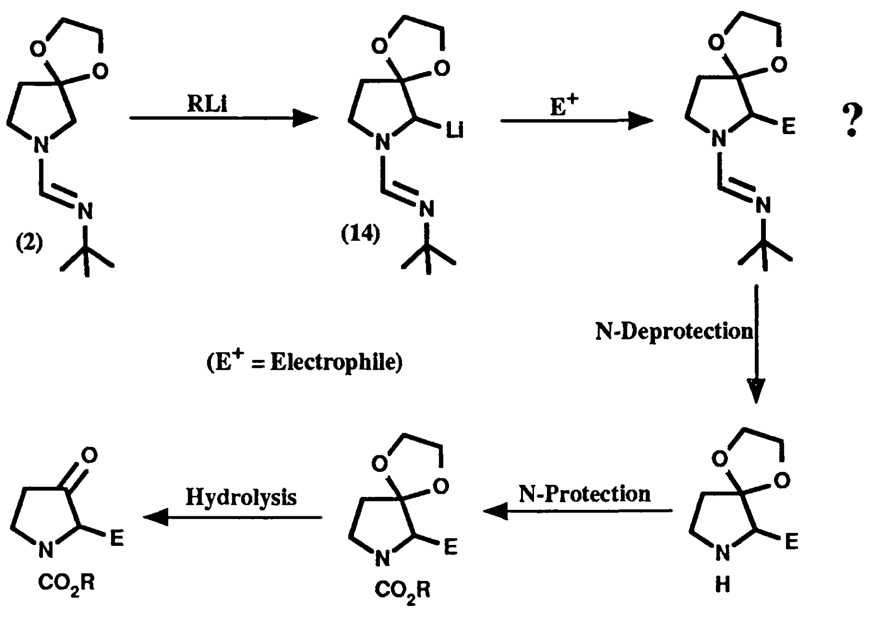
The preparation of amine **(1)**, required for the attempted synthesis of **(3)**, involved condensation of the sodium salt of *N*-ethoxycarbonyl glycinate[121] with ethyl acrylate to give the crystalline β-keto ester **(4)**[122] *via* a Dieckmann cyclization (Scheme 6). Amine **(1)** was derived from **(4)** *via* ketone **(5)** and ketal **(6)** according to the procedures described by Bühler and Viscontini.[114] The method developed by Meyers *et al*[115a] for the conversion of secondary amines to the corresponding formamidine derivatives was employed to prepare the novel formamidine **(2)** in 83% yield from **(1)** (Scheme 7). Hydrolysis of the ketal group of **(2)** was now required to produce the desired 3-pyrrolidinone **(3)**. However, all attempts at acid-catalyzed hydrolysis of **(2)** led to decomposition and none of the desired product was isolated. A non-hydrolytic ketal cleavage was next considered as a means of releasing the ketone under relatively mild conditions. Accordingly, the corresponding dimethyl ketal derivatives **(7)**-**(10)** were prepared in a straightforward manner as shown in Scheme 8. The iodotrimethylsilane-mediated cleavage[123,124] of the ketal moiety of formamidines **(9)** and **(10)** was investigated and while **(9)** decomposed under these conditions, a low yield of a carbonyl-containing compound was obtained from **(10)**. The IR and ^{1}H nmr spectra of this material were consistent with structure **(11)** (Scheme 9), however, the 3-pyrrolidinone **(11)** deteriorated over several hours on standing at room temperature, and the instability of this product precluded further characterization. Thus, it appeared that 3-pyrrolidinones such as **(3)** and **(11)** would be neither synthetically useful, nor indeed readily accessible.



Scheme 9



Scheme 10

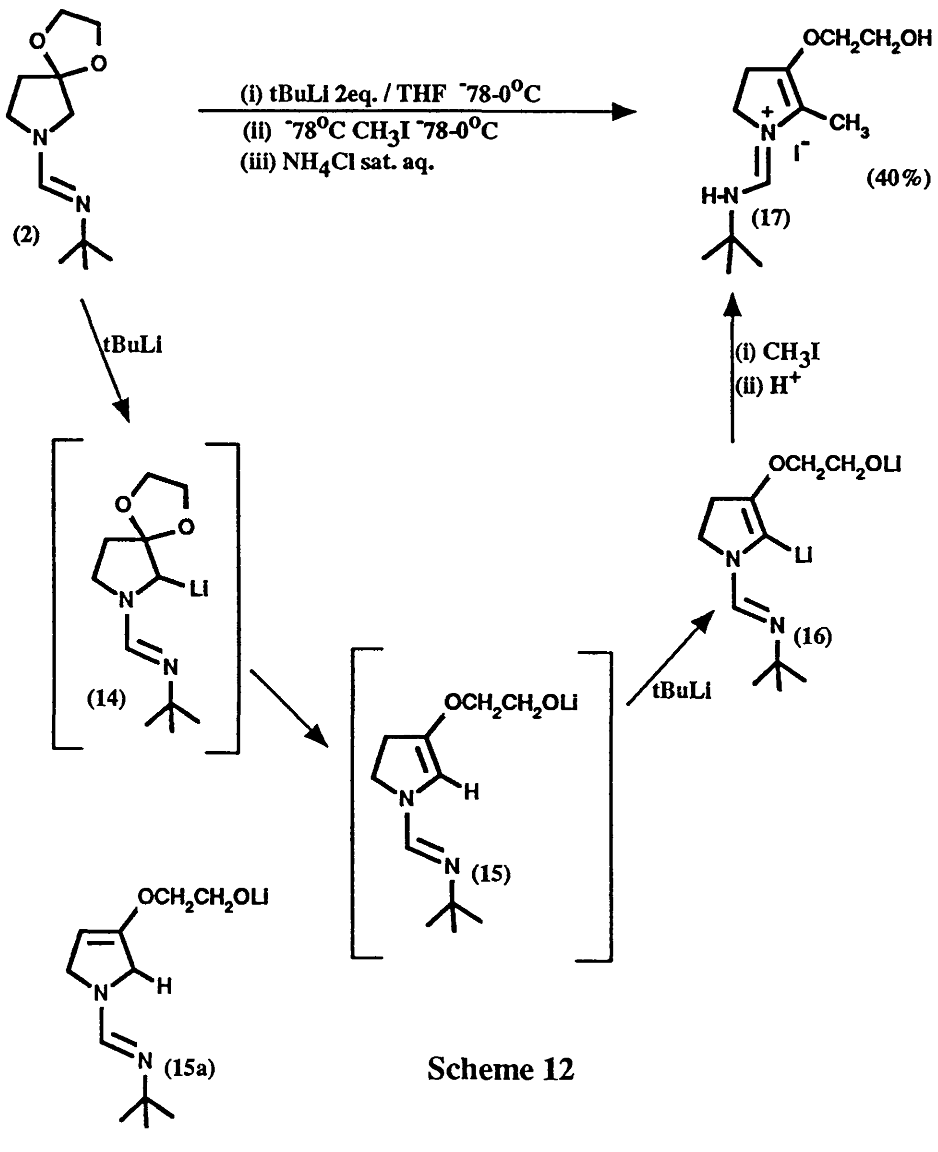


Scheme 11

An attempt was made to circumvent these problems by employing a less basic activating group attached to the ring nitrogen atom. The urea **(13)** was prepared by acylation of amine **(1)** and subsequent hydrolysis of the ketal **(12)** (Scheme 10). In contrast to the ketal derivatives in the formamidine series, acid hydrolysis of the ketal **(12)** proceeded smoothly to liberate the ketone function and provide urea **(13)**. Ureas have previously been used by Seebach *et al* for the generation of α-lithio-amine synthetic equivalents.[125] Unfortunately, attempts to prepare the lithium enolate of **(13)** were unsuccessful and, for reasons that are not clear, **(13)** suffered complete decomposition upon treatment with LDA at -78°C.

1.1.2 The Metalation-Elimination-Metalation Reaction of Ketals - Preparation and Electrophilic Substitution of a β-Lithiated Enol Ether

Since our efforts to generate C-2 enolates directly from *N*-substituted 3-pyrrolidinones had met with failure, we turned our attention to the lithiation of formamidine ketal (2). We anticipated that lithiation at C-2 or at C-5 would occur if (2) were to be treated with an alkyllithium base according to the conditions described by Meyers.[115a] (Scheme 11). Furthermore, the protons at C-2 should be kinetically more acidic owing to the inductive effect of the β-oxygen atoms of the ketal moiety. Therefore, kinetic deprotonation of (2) with an alkyllithium base should proceed to give **(14)**, and if this species were to be trapped with electrophiles, subsequent transprotection of the heterocyclic nitrogen atom followed by ketal hydrolysis would lead to the required 2-substituted-3-pyrrolidinones. In this way, organolithium **(14)** would function as a synthetic equivalent of a regiospecific 3-pyrrolidinone enolate.



Scheme 12

In the event, treatment of **(2)** with two equivalents of *tert*-butyllithium in THF followed by the addition of iodomethane and protic work-up afforded the crystalline hydrogen iodide salt **(17)** in 40% yield (Scheme 12). A plausible mechanism to account for the formation of **(17)** is outlined in Scheme 12. Initial deprotonation of **(2)** at C-2 gives the α-lithiated formamidine **(14)**, as expected, but this species undergoes rapid β-elimination of alkoxide to give enol ether **(15)**; a related elimination process involving a dithioketal derivative has been observed by Meyers and co-workers.[(126)] Consideration of the mechanistic features associated with such formamidine-directed deprotonations and the nature of the nucleofuge in the substrate **(2)** has led us to invoke an $ElcB_I$ mechanism[(160)] for this elimination, although we have no evidence to support this proposal. Metalation of **(15)** *via* abstraction of the acidic olefinic proton by a second equivalent of base gives dianion **(16)** which undergoes alkylation by iodomethane at the carbanionic centre. Finally, protonation of the exocyclic formamidine nitrogen atom in the presence of iodide ion gives rise to the observed product **(17)**, which exists as a single geometrical isomer (presumably the E-isomer; see below) about the exocyclic double bond.

Several features of this reaction are worthy of comment. Firstly, the manner in which **(15)** is generated rules out the possibility of contamination from the isomeric enol ether **(15a)**, which is not observed, and hence organolithium **(16)** and the product **(17)** are obtained in isomerically pure form. This is in contrast to the preparation of enol ethers *via* enolization of *N*-substituted-3-pyrrolidinones which, in general, leads to mixtures of isomers[(84)] (see Introduction, Section 3.2). Secondly, the generation of an intermediate **(15)** which is more acidic than the starting material **(2)** necessitates the use of a minimum of two equivalents of base for the complete conversion of **(2)** to the dianion **(16)**. Thirdly, the alkylation of the lithiated enol ether **(16)**

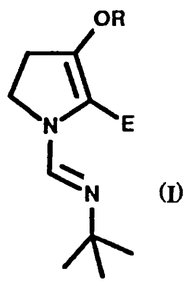
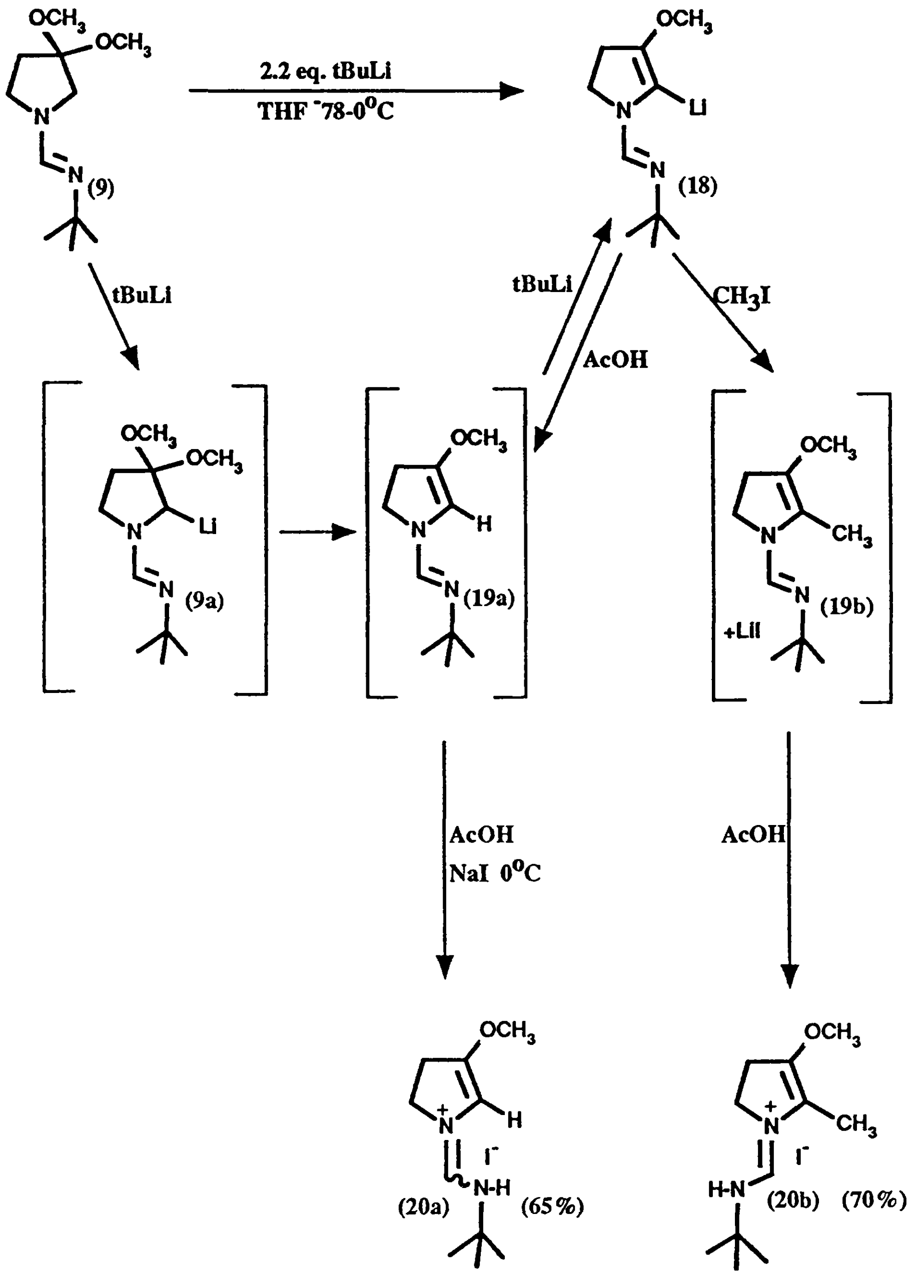


Fig. 1



Scheme 13

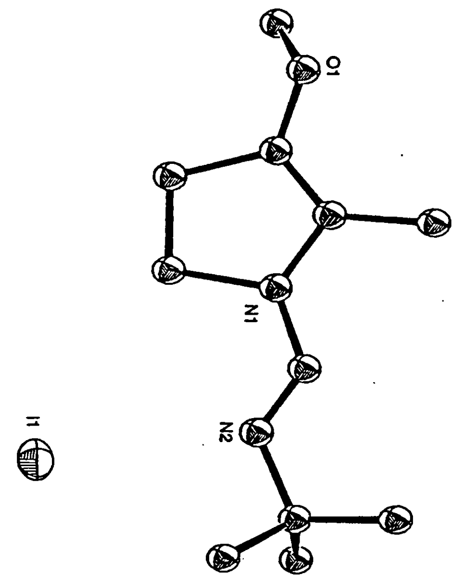
constituted the substitution of the heterocycle at C-2, as required. Finally, the ketone oxidation level at C-3 of the starting material has been maintained in the product. These features suggested that the overall process held considerable promise for our requirements. However, in order to study the scope of the process for the preparation of 2-substituted-3-alkoxy-$\Delta^{2,3}$-pyrrolines **(I)** (Fig. 1), a somewhat simpler anionic system lacking the oxidoethyl group of **(16)** was desirable. Accordingly, the lithiation conditions were applied to formamidine **(9)**, possessing a simple dimethyl ketal unit, and the resulting monoanionic organolithium **(18)** was found to undergo smooth methylation, as expected, to give the 2-methyl derivative **(19b)** which was isolated as the crystalline hydrogen iodide salt **(20b)** in 70% yield (Scheme 13). Protonation of **(18)** followed by protic work-up in the presence of sodium iodide gave hydrogen iodide salt **(20a)** as a crystalline solid in 65% yield *via* the free base **(19a)**, which is also presumably an intermediate in the formation of **(18)**. Attempts to trap putative intermediate **(9a)** were unsuccessful.

The metalation-elimination-metalation sequence employed for the generation of organolithium **(18)** from formamidine ketal **(9)** constitutes a novel method for the preparation of organolithiums of this type, which were previously unknown in the literature. The corresponding formal elimination of methanol from cyclic ketals *via* Lewis-acid promoted cleavage has been reported.[127] The final conversion of **(19a)** to organolithium **(18)** is an example of an α-heteroatom-facilitated lithiation, wherein the acidity of the olefinic proton is enhanced by the presence of the α-heteroatom, in this case the heterocyclic nitrogen atom. Gschwend and Rodriguez have reviewed the subject of heteroatom-facilitated lithiations[128] and there have been a number of recent studies on the α-metalation of enol ethers.[129] The molecular orbital calculations performed by Gould *et al* suggest that the enhancement of the kinetic acidity of olefinic substrates by an α-heteroatom results from population

(II)

(III)

Fig. 2



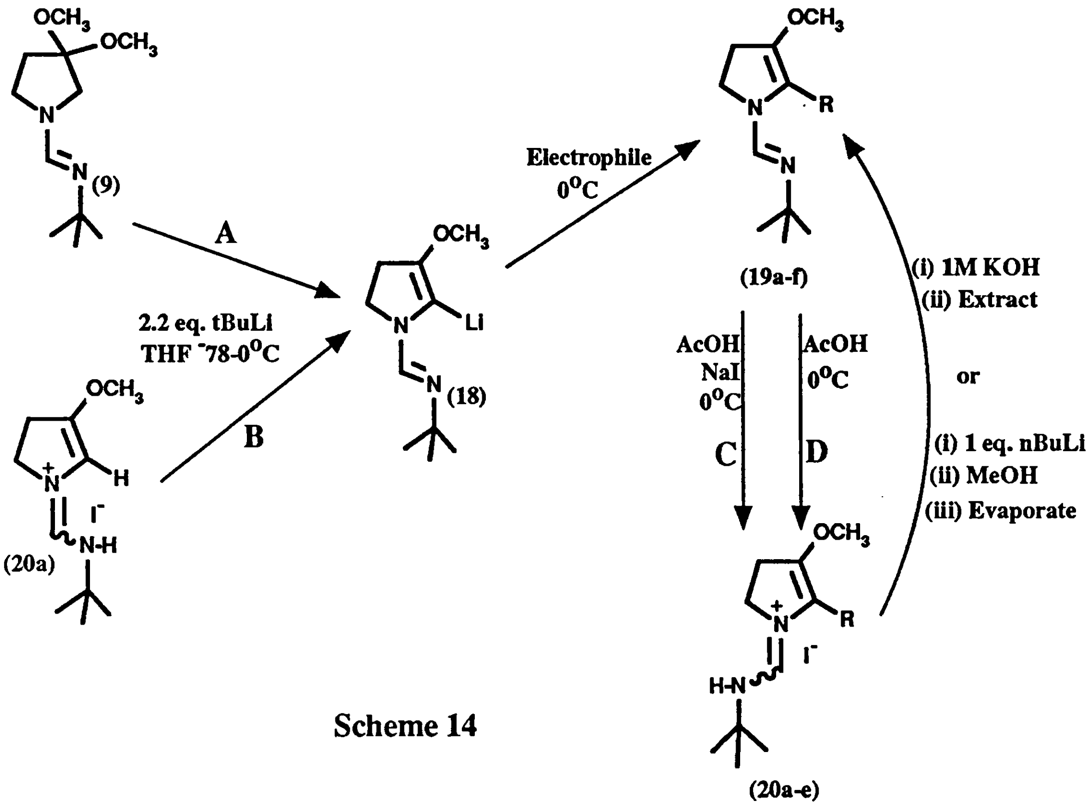
ORTEP PLOT OF (20b)

Fig. 3

of the antibonding σ^* orbital of the adjacent olefinic carbon-hydrogen bond by lone pair electrons formally associated with the heteroatom.[130] However, the organolithium **(18)** is both an α-lithiated enamine[131] <u>and</u> a β-lithiated enol ether (see Introduction, Section 3.7) and the effect of the β-oxygen atom on the kinetic acidity of the olefinic proton of the precursor **(19a)** might be expected to complement that of the α-nitrogen atom, by analogy with the enhanced kinetic acidity of **(II)** compared to **(III)**[129d] (Fig. 2). The lithiation of olefinic molecules containing both α- and β-oxygen atoms has been reported by several workers.[109,111,132]

With a convenient method for the preparation of organolithium **(18)** now available, the range of electrophiles with which this species would react was of obvious interest. Therefore, an investigation into the reactivity of **(18)** towards a variety of electrophiles was undertaken. Before the results of this study are discussed, several considerations regarding the isolation and characterization of the hydrogen iodide salts **(20a)** and **(20b)** deserve comment.

Although the free bases **(19a)** or **(19b)** could be obtained from **(18)** *via* protonation or methylation respectively, it was found that formation of the corresponding hydrogen iodide salts **(20a)** and **(20b)** aided the isolation of these compounds. These salts could be chromatographed on silica gel using chloroform-methanol solvent systems as eluants and any non-ionic impurities were removed in the early fractions under these conditions. Furthermore, the salts **(20a)** and **(20b)** were both highly crystalline and the structure of the 2-methyl derivative **(20b)** was confirmed by single crystal X-ray analysis. This revealed that **(20b)** existed exclusively as the E-isomer and the iminium tautomer in the solid state (Fig. 3). The ^1H nmr spectrum of the 2-protio derivative **(20a)** revealed that this salt existed a 3:2 mixture of E/Z isomers which were not assigned. The hydrogen iodides were found to be ideal



Scheme 14

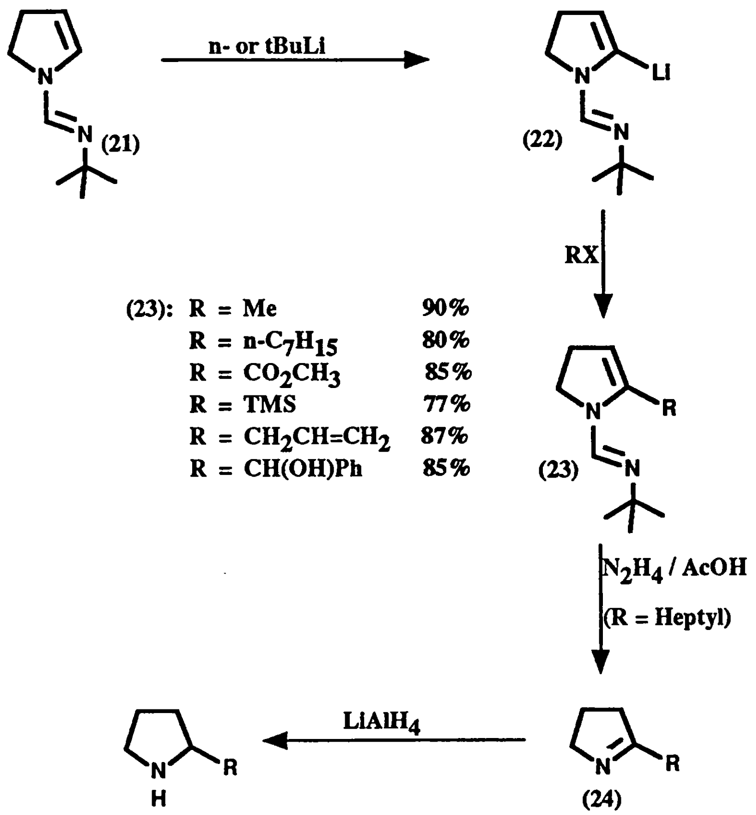
Table 1

Procedure	Electrophile	Adduct	Isolated Product	R =	Yield %
A,C	AcOH	(19a)	(20a)	H	65
A,D	CH_3I	(19b)	(20b)	CH_3	70
B*,D	n-$C_5H_{11}Br$	(19c)	(20c)	n-C_5H_{11}	23
A,C	$PhCH_2Br$	(19d)	(20d)	CH_2Ph	14
A,C	n- $C_5H_{11}CHO$	(19e)	(20e)	$CH(OH)C_5H_{11}$	78
A	PhCHO	(19f)	(19f)	CH(OH)Ph	87

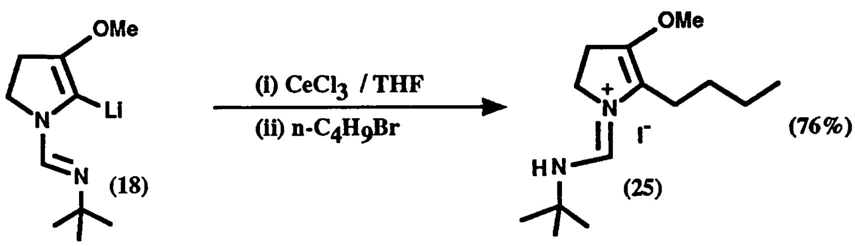
* The solution of (18) was recooled to $^-78^oC$ and 1.55eq. of TMEDA was added prior to the addition of 1-bromopentane.

substrates for characterization by FAB mass spectrometry, yielding both positive and negative (iodide) FAB ionization profiles. The products obtained from the ensuing study of the reactivity of organolithium **(18)** towards electrophilic reagents were generally isolated and characterized as the formamidine hydrogen iodide salts.

The results of this study are presented in Scheme 14 and Table 1. Organolithium **(18)** could be generated either from **(9)** (Method A) or from **(20a)** (Method B), and in general, it was found most convenient to start with the ketal **(9)**. Reaction of **(18)** with electrophiles gave the adducts **(19a-f)** from which hydrogen iodide salts **(20a-e)** were obtained by direct treatment with acetic acid and sodium iodide (Method C), or with acetic acid alone where the reaction mixture already contained an equivalent of iodide ion (Method D). Adduct **(19f)** was isolated as the free base, and the free bases **(19a-e)** could be obtained from the corresponding acid salts by treatment with potassium hydroxide or *n*-butyllithium, as shown in Scheme 14. From the results presented in Table 1, it is evident that the organolithium reagent **(18)** reacted smoothly with aldehydes, including hexanal, an enolizable aldehyde, to give high yields of adducts. However, the alkylation of **(18)** with alkyl halides other than iodomethane was inefficient. For example, reaction of **(18)** with 1-bromopentane afforded only a low yield of alkylated material **(20c)**, and although the addition of TMEDA[(133)] (1.55 equivalents) to the reaction mixture appeared to enhance the alkylation to a small extent, no significant improvement in yield could be realized using a range of different solvents, co-solvents and temperature ranges, or by substituting the bromoalkane for the corresponding iodoalkane. Varying quantities of **(20a)** were recovered from these reactions. Similarly, reaction of **(18)** with benzyl bromide gave low yields of alkylated adduct **(20d)**, and significant quantitites of 1,2-diphenylethane were isolated together with recovered **(20a)**. It is of interest to compare these results



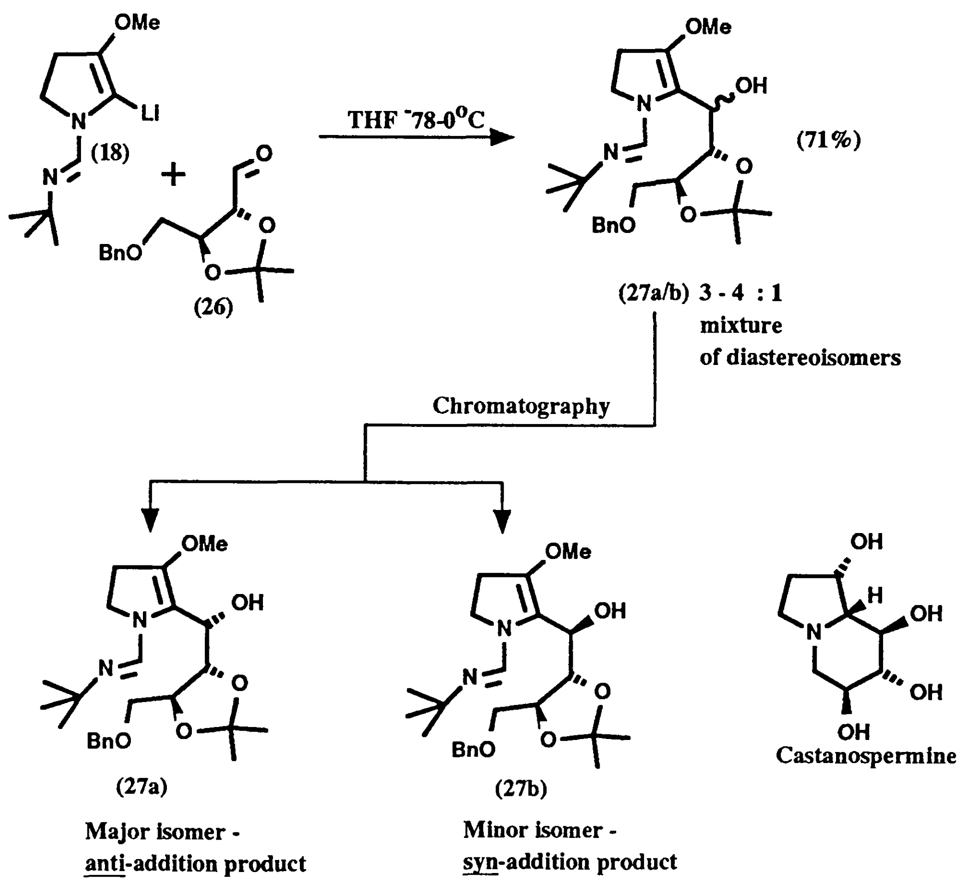
Scheme 15



Scheme 16

with those obtained by Meyers *et al* for the alkylation of the organolithium **(22)** derived from the simple eneamidine **(21)**, which lacks the 3-methoxy group of **(19a)**[133] (Scheme 15). These workers found that organolithium **(22)** reacted smoothly with a variety of electrophiles, including alkyl halides, to give high yields of adducts. However, the alkylation of **(22)** with allyl bromide only proceeded efficiently when the pentynylcuprate derivative was first generated, a tactic employed previously by Meyers to suppress undesirable electron-transfer processes which were observed in related alkylations.[115a] The preparation of substituted derivatives **(23)** (R = allyl, benzyl, alkenyl) has been recently reported by Terashima and Ishikura, *via* reaction of the triethylborate derivative of **(22)** with electrophiles in the presence of copper (I) ion.[134]

The reactivity of **(18)** may be influenced by the 3-methoxy group, which provides an extra site for intra- and intermolecular coordination with the lithium, and is also likely to exert significant effects on the electronic nature of this species, including enhanced π-electron density at C-2, relative to **(22)**. Alkylation of **(18)** with 1-bromobutane was eventually achieved *via* the organocerium derivative,[135] and the 2-butyl derivative **(25)** was obtained in 76% yield[136] (Scheme 16). It is not clear whether this improved alkylation protocol owes its success to the low basicity associated with organocerium reagents,[137] which should discourage competing elimination processes, or to the suppression of some other side reactions. The use of copper (I) iodide[110b,129b] in these reactions resulted only in marginal increases in yield for alkylation of **(18)** with benzyl bromide and 1-bromobutane.[136] These areas may be worth further investigation.


OMe
Li
N
N
(18)
+
O
BnO
O
O
(26)
THF -78-0°C
OMe
OH
N
N
O
BnO
O
(71%)
(27a/b) 3 - 4 : 1
mixture
of diastereoisomers
Chromatography
OMe
OH
N
N
O
BnO
O
(27a)
Major isomer -
anti-addition product
OMe
OH
N
N
O
BnO
O
(27b)
Minor isomer -
syn-addition product
OH
H
OH
N
OH
OH
Castanospermine

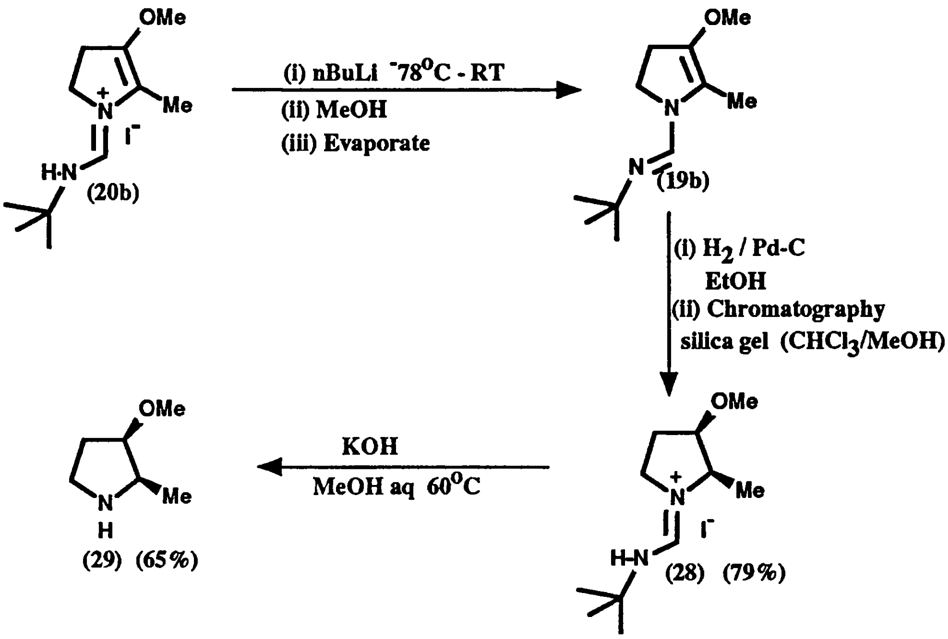
Scheme 17

1.1.3 Addition of the β-Lithiated Enol Ether to a Chiral Aldehyde

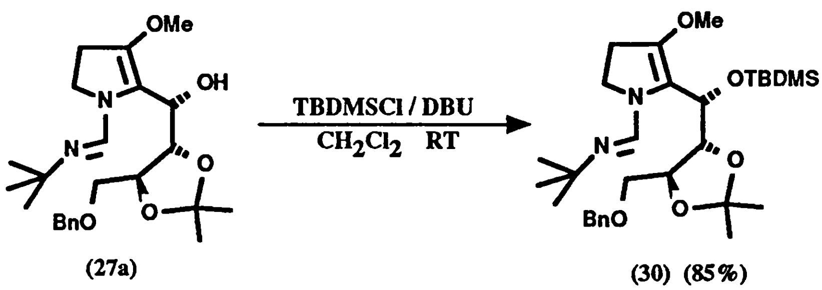
In conjunction with these studies on the scope and limitations of organolithium **(18)** as a nucleophilic unit, the application of this chemistry to the synthesis of our target molecule, castanospermine, was pursued. Encouraged by the efficient condensation of **(18)** with hexanal, we envisioned the addition of this reagent to a more complex, chiral aldehyde, possessing a suitably oxygenated carbon chain. Accordingly, the known chiral aldehyde **(26)** was prepared in five steps[138] from L-tartaric acid and reacted with **(18)** to give a mixture of diastereoisomeric adducts **(27)**, in a ratio of 3-4:1 depending on the run, and in 71% yield (Scheme 17). The hydrogen iodide salts of these adducts were not prepared. Separation of the diastereoisomers was accomplished by silica gel chromatography and the adducts crystallized upon storage at -20°C and recrystallization (see Experimental) afforded the pure diastereoisomers as colourless needles. Although the absolute stereochemistry at the newly formed stereogenic centre of each isomer could not be determined from the available spectroscopic data, the major isomer was tentatively assigned as the *anti*-addition product **(27a)**. This was based on the precedent established by Mukaiyama and coworkers, who demonstrated that the non-chelation controlled addition of organolithium reagents to **(26)** proceeded in an *anti*-selective manner.[138,139]

1.1.4 The Attempted Deprotection of the Enol Ether Adducts

Before any further chemical manipulation of **(27a)** and **(27b)** was attempted, the problem of *N*-deprotection and cleavage of the enol ether moiety of the adducts featured in Table 1 had first to be addressed. Because of the previously observed incompatibility of the ketone function with the formamidine group, direct hydrolysis of the enol ether moiety was not expected



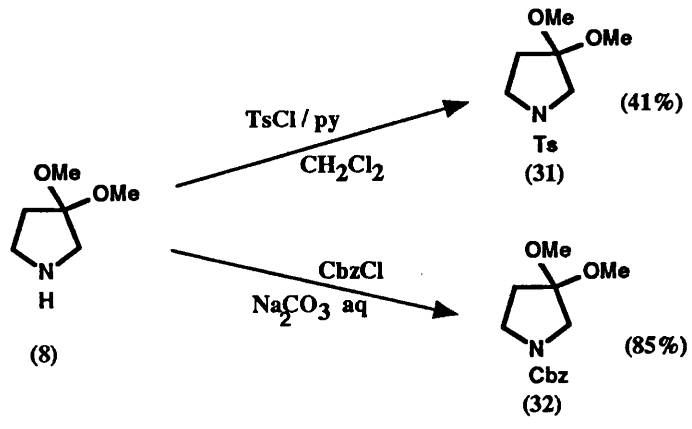
Scheme 18



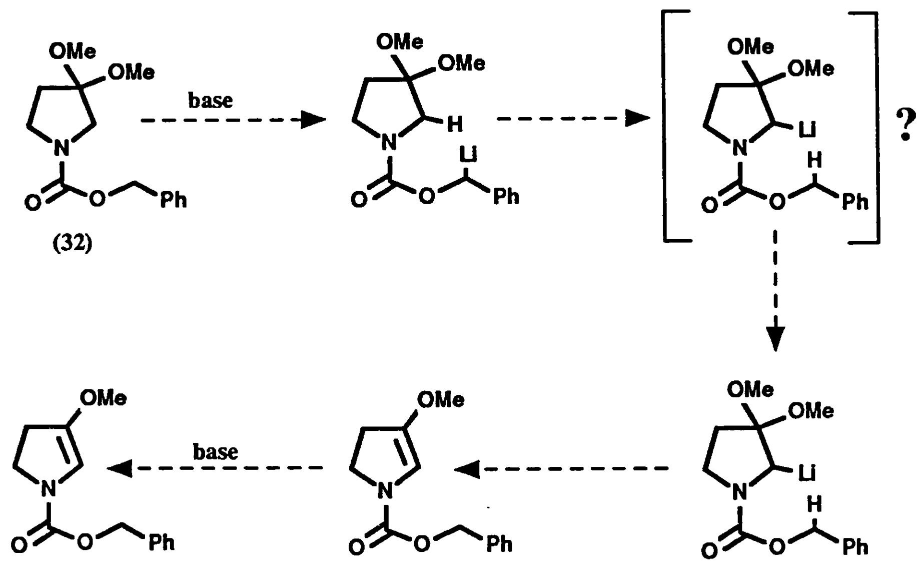
Scheme 19

to prove fruitful. The complex mixture of products obtained and the substantial material loss observed upon the attempted iodotrimethylsilane-mediated[140] cleavage of **(20b)** confirmed these suspicions. Somewhat surprisingly, endeavours to deprotect the heterocyclic nitrogen atom, and thereby obtain the cyclic imines corresponding to **(24)** (see Scheme 15), failed to yield any isolable products, and even the simple methyl derivative **(19/20b)** decomposed when exposed to the hydrolytic *N*-deprotection protocols described by Meyers.[115a,133] These reactions were attempted on both hydrogen iodide salts and free bases alike but without success, and the aldehyde adducts **(19/20e)** and **(19/20f)** were found to be particularly sensitive to chemical manipulations.

In contrast, cleavage of the formamidine unit of the saturated derivatives of the 2-alkylated heterocycles was facile, and this was exemplified by the alkaline hydrolysis[115a] of formamidine **(28)**, prepared *via* catalytic hydrogenation of the 2-methyl-substituted free base **(19b)** (Scheme 18). The hydrolysis of **(28)** resulted in smooth *N*-deprotection and the 2-methyl-3-methoxy pyrrolidine **(29)** was obtained in 51% overall yield from **(20b)**. An attempt to confirm the *cis*-stereochemistry of **(29)** using an n.O.e. experiment was inconclusive. Thus, when the endocyclic double bond is reduced, these formamidine derivatives behave as expected, however, the required oxidation level at C-3 is lost and so the organolithium **(18)** cannot be regarded as a synthetic equivalent of a 3-pyrrolidinone C-2 enolate. Nevertheless, hydrogenation of the chiral adducts **(27a)** and **(27b)** should have allowed further chemical operations to be performed with a view to the assembly of indolizidines related to castanospermine. Unfortunately, complete decomposition of these adducts was observed upon exposure to the standard catalytic hydrogenation conditions and the loss of starting material in these reactions was accompanied by the production of many unidentified products. Similar results were obtained from a number of experiments performed on these



Scheme 20



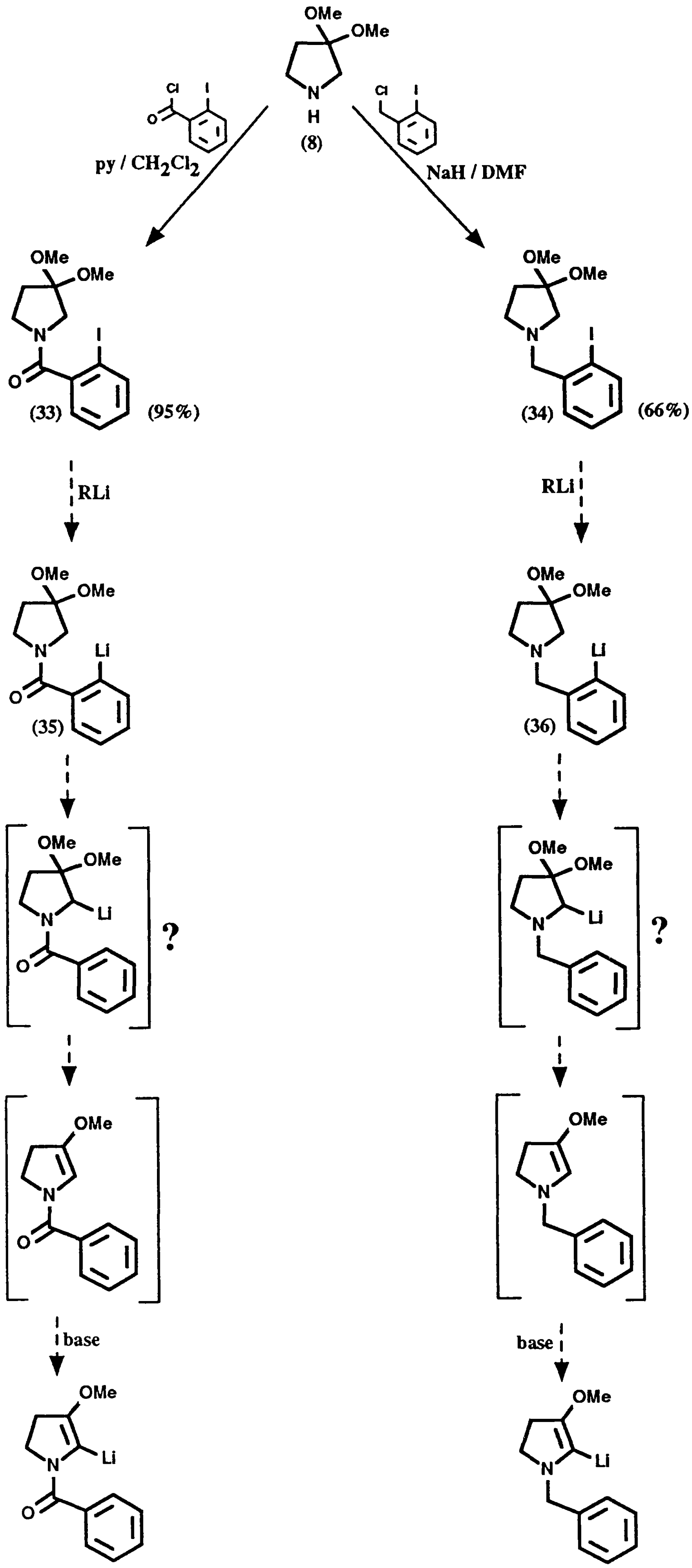
Scheme 21

sensitive adducts. The *O*-silylation of **(27a)** was the only successful reaction of those attempted involving either diastereoisomer (Scheme 19), but the product **(30)** appeared to offer no advantages over **(27a)** in terms of stability. It is probable that the instability of the aldehyde adducts stems from the sensitivity of the δ-hydroxy enol ether functionality present in these derivatives (see Sections 1.3.2 and 1.3.3).

1.2 The Lithiation of Systems with Alternative Nitrogen-Substituents

1.2.1 N-*Benzyloxycarbonyl and* N-*Tosyl Derivatives*

The failure to express the equivalence of organolithium **(18)** to a 3-pyrrolidinone C-2 enolate and the sensitivity of the derived adducts renders this species obsolete as a useful nucleophilic unit. The search for an analogous organometallic reagent with peripheral functionality lacking the basic and nucleophilic characteristics associated with the formamidine group was resumed, a major requirement being the ability to expose the ketone function at C-3 after incorporation of the C-2 substituent. To this end, the toluene-p-sulphonamide **(31)** and the *N*-benzyloxycarbonyl derivative **(32)** were prepared in a straightforward fashion (Scheme 20). Reaction of these substrates with organolithium reagents was examined in order to ascertain whether a metalation-elimination-metalation sequence could be initiated as found in the formamidine series. With carbamate **(32)** an interesting possibility was the abstraction of an acidic benzylic proton[109,132a] and a subsequent proton transfer giving the required C-2 lithiation and leading ultimately to the desired alkenyllithium reagent as depicted in Scheme 21. When a colourless solution of carbamate **(32)** in THF was treated with *tert*-butyllithium at -78°C a deep red solution was produced and analysis of the reaction mixture by TLC revealed that many products were present, none of which could be isolated cleanly.



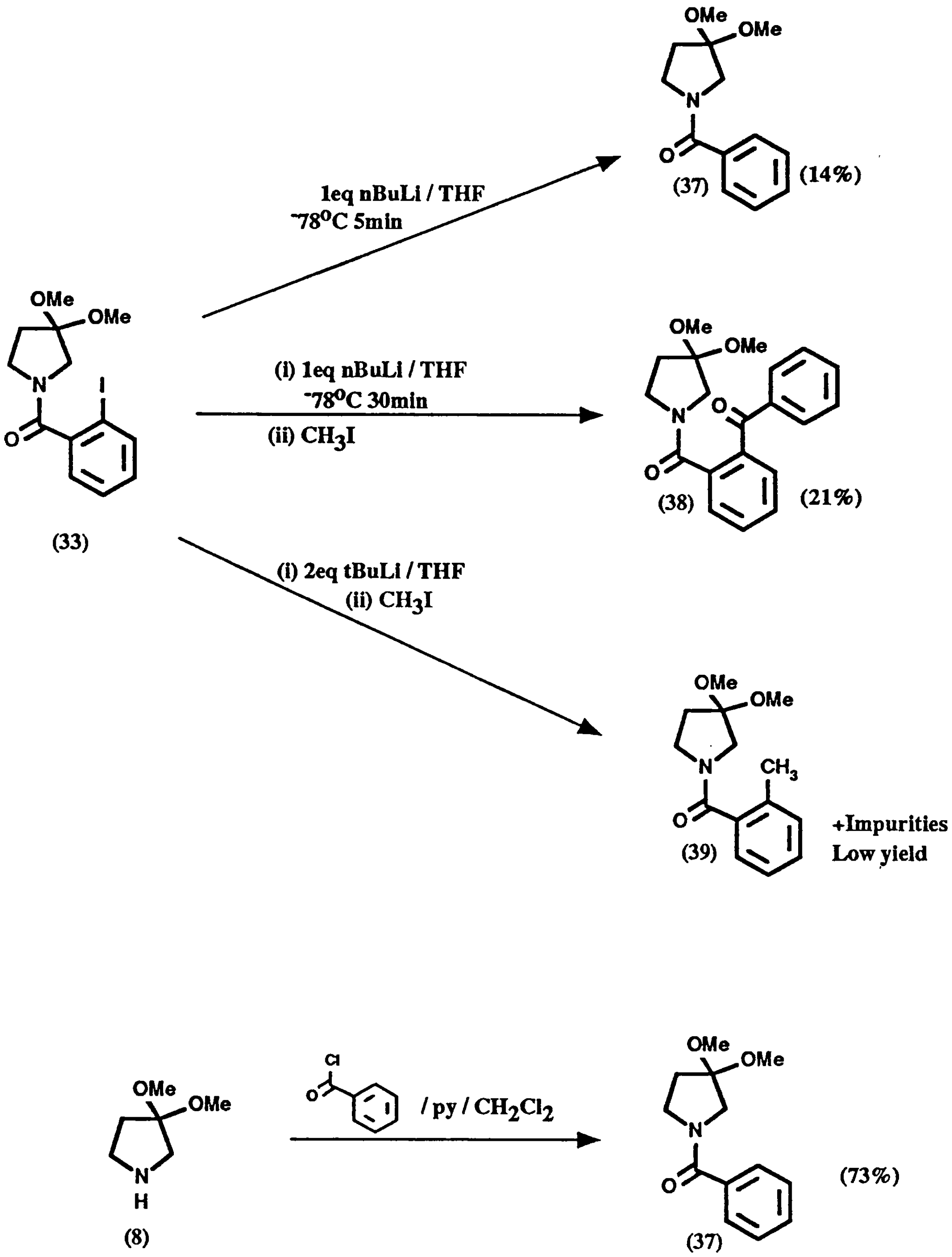
Scheme 22

Similarly, no products could be isolated from the reaction the sulphonamide **(31)** with either *n*-butyllithium or *tert*-butyllithium. It is possible that these reagents attacked the sulphur atom of the sulphonamide linkage[141] in **(31)** or the carbonyl group of the carbamate[142] in **(32)**. Alternatively, the benzylic anion derived from **(32)** could undergo preferential intermolecular acylation or acyl-Wittig rearrangement reactions of the type reported for the benzyl anion of benzyl benzoate.[143]

1.2.2 Systems with Lithiated Nitrogen-Substituents

The idea of an internal organolithium base initiating the ketal alkoxide elimination reaction was particularly attractive, and an alternative means of generating such a species was sought. Since aryl iodides are useful precursors to aryllithium species *via* halogen-metal exchange with an alkyllithium reagent,[144] the *o*-iodobenzamide **(33)** and the *o*-iodobenzylamine **(34)**, prepared as shown in Scheme 22, should allow access to the aryllithium derivatives **(35)** and **(36)** respectively. *o*-Lithiated benzamides have been prepared previously *via* halogen-metal exchange[144a,b] and there is evidence to suggest that these exchange reactions are extremely fast so that direct attack of the alkyllithium reagent on the carbonyl group of **(33)** should be avoidable.[144a] A subsequent proton transfer from C-2 of the pyrrolidine ring to the pendant aryllithium moiety of **(35)** and **(36)**, followed by elimination and metalation should give the desired alkenyllithium reagents as shown in Scheme 22. Such a 1,5-proton transfer[145] would constitute the ionic equivalent of the known aryl-to-α-amidoyl 1,5-radical translocation reaction.[146]

When the iodobenzamide (33) was treated with one equivalent of *n*-butyllithium at -78°C and the reaction mixture was quenched after five minutes, a low yield of the deiodinated product **(37)** was isolated, the identity of

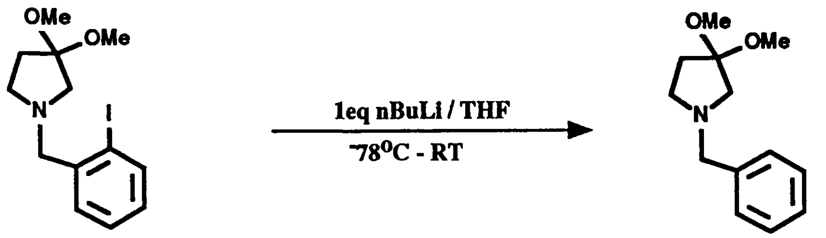

OMe
OMe
N
O
(37)
(14%)
1eq nBuLi / THF
-78°C 5min
(33)
I
(i) 1eq nBuLi / THF
-78°C 30min
(ii) CH3I
(38)
(21%)
(i) 2eq tBuLi / THF
(ii) CH3I
CH3
(39)
+Impurities
Low yield
H
(8)
Cl
/ py / CH2Cl2
(73%)

Scheme 23

which was confirmed by independent synthesis from **(8)** (Scheme 23). A subsequent attempt to trap the aryllithium intermediate with iodomethane resulted only in the isolation of the *o*-benzoylbenzamide **(38)** in 21% yield. However, when the experiment was repeated using two equivalents of *tert*-butyllithium in place of the *n*-butyllithium, a mixture of products were isolated which was analyzed by ^1H nmr spectroscopy and mass spectrometry. The singlet resonance at δ 2.17 in the ^1H nmr spectrum and the intense molecular ion peak at m/z 249 in the mass spectrum indicated that the methylated derivative **(39)** was present in this mixture. Products resulting from benzoylation of the intermediate aryllithium, such as **(38)**, were probably also present in the mixture since the integral for the aromatic resonance in the ^1H nmr spectrum was abnormally high. The methyl adduct **(39)** may also have been produced in the former of these two trapping experiments, but this product was probably lost during the repeated silica gel chromatography required for the purification of **(38)**.

These results suggest that the aryllithium species **(35)** is generated *via* iodine-lithium exchange, and that this species does not suffer intramolecular proton transfer but undergoes intermolecular acylation, presumably *via* self-condensation. This type of *o*-benzoylation process has been observed by Parham and Bradsher during the reactions of methyl *o*-bromobenzoate with *n*-butyllithium,(147) and the formation of *o*-benzoyl-*N,N*-diethylbenzamide *via* acylation of a deprotonated species by unmetalated amide has been reported by Beak and coworkers.(148)

The halogen-metal exchange reaction of *o*-iodobenzylamine **(34)**, which lacks the conformational restrictions associated with the amide unit of **(33)**, was next examined. When one equivalent of *n*-butyllithium was added to a solution of **(34)** in THF at -78°C and the reaction mixture was allowed to

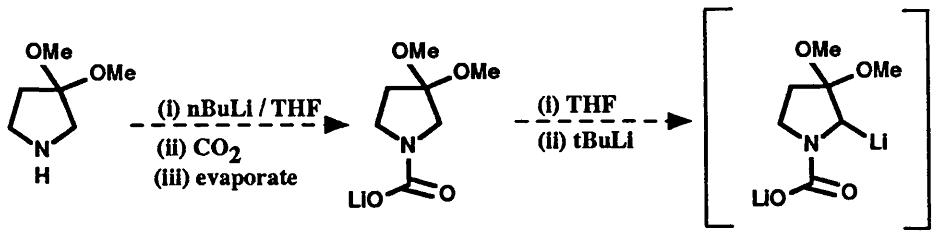


(98%)

34) → 5 (35)

(40)

Scheme 24



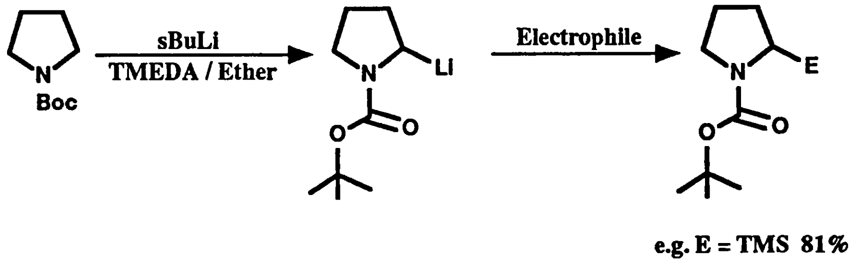
Scheme 25

warm slowly to room temperature, no elimination products were observed, but the deiodonated benzylamine **(40)** was isolated in 98% yield (Scheme 24). Presumably, the intermediate aryllithium **(36)** is formed but again fails to undergo proton transfer.

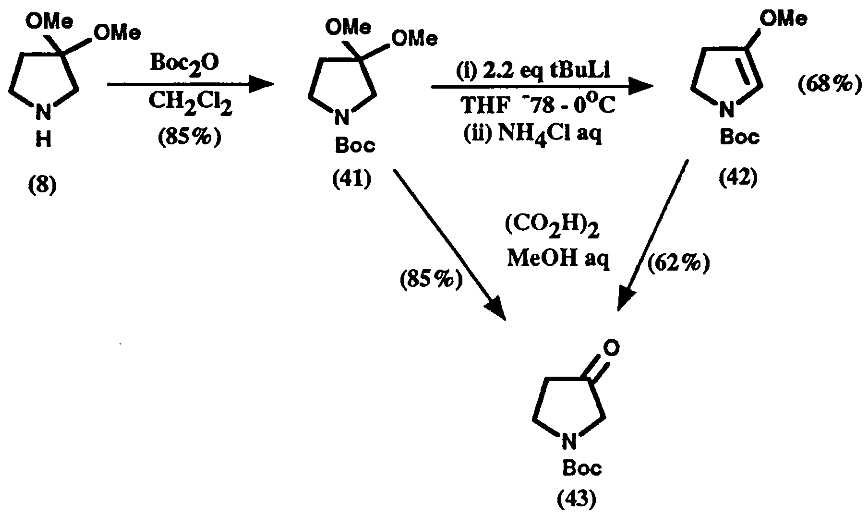
The pendant aryllithium groups of **(35)** and **(36)** may not be capable of adopting a suitable orientation for deprotonation of the pyrrolidine ring at C-2, and in any case, the acidity of the C-2 protons may be too low for the generation of significant equilibrium concentrations of C-2 lithiated species, necessary for methoxide elimination *via* an $ElcB_R$ mechanism.[160]

A brief investigation into the application of the methodology developed by Katritzky and coworkers[149] to the α-lithiation of amine **(8)**, *via* the lithio carbamate derivative was undertaken (Scheme 25). Katritzky *et al* have shown that this method is useful for the preparation of 1-lithiated tetrahydroisoquinolines[149a] and 2-lithiated indoles[149b], however, no useful products were isolated when the method was applied to **(8)**.

These approaches were abandoned at this stage in favour of an alternative method for the α-lithiation of carbamates.



Scheme 26



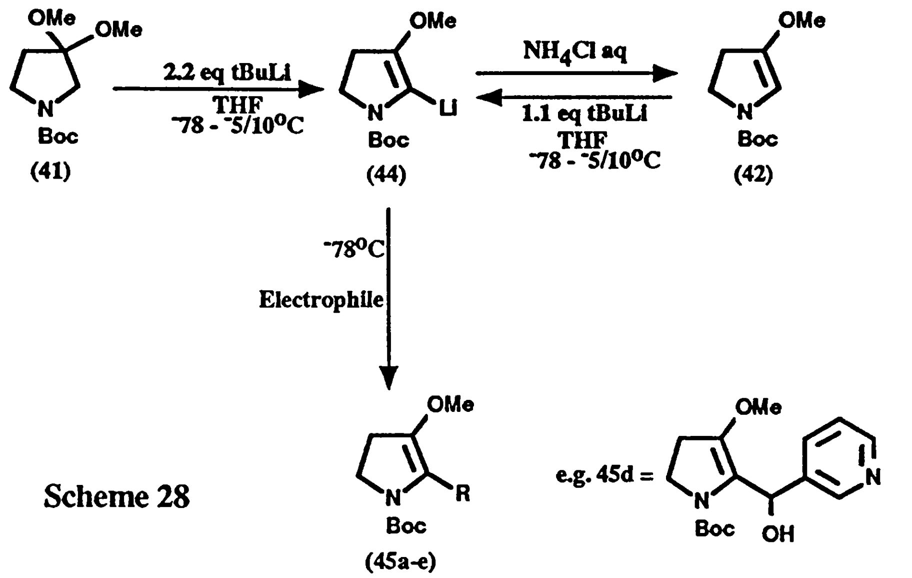
Scheme 27

1.3 *The Deprotonation of Carbamate Derivatives*

1.3.1 *The* N-*Boc Directed Metalation-Elimination-Metalation Reaction - Preparation and Electrophilic Substitution of a* β-*Lithiated Enol Ether*

During the course of our studies on the generation of organolithium reagents as 3-pyrrolidinone enolate equivalents, we became aware of some work carried out by Professor Beak at the University of Illinois, involving the use of the *tert*-butoxycarbonyl (Boc) group as an activating group for the α-lithiation of carbamates.[(150)] This work was duly published as a communication[(151)] and the methodology involved is shown in Scheme 26. The overall C-2 substitution process is directly analogous to that described by Meyers and coworkers using formamidines as directing groups (see Section 1.1), since the intermediate organolithium species is dipole-stabilized.[(116)] In this case, both the starting material and the product are devoid of a basic or nucleophilic nitrogen atom. Therefore, the Boc group appeared to be an ideal candidate for replacement of the formamidine unit in the metalation-elimination-metalation process.

The requisite starting material **(41)** was prepared by *N*-protection of amine **(8)** (Scheme 27). Gratifyingly, ketal **(41)** suffered smooth elimination of methanol upon treatment with *tert*-butyllithium (2.2 equivalents) in THF, to give, after protic work-up, the enol ether **(42)** as a crystalline solid in 68% yield. A characteristic feature in the ^{1}H nmr spectrum of **(42)** was the shape of the resonance due to the olefinic proton, which consisted of two 0.5H singlets at δ 5.76 and δ 5.92. Presumably, this arises because of restricted rotation about the exocyclic nitrogen-carbon bond (amide-type resonance).



Scheme 28

Table 2

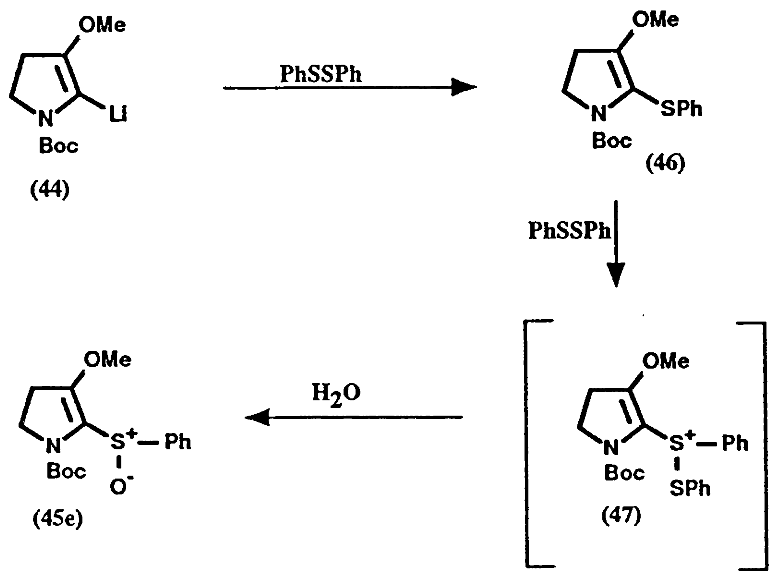
Product	Electrophile	R =	Yield %
(45a)	PhCHO	CH(OH)Ph	42
(45b)	n-$C_5H_{11}CHO$	$CH(OH)C_5H_{11}$	40
(45c)	$(CH_3)_2CHCHO$	$CH(OH)CH(CH_3)_2$	42
(45d)	3-C_5H_4NCHO	$CH(OH)C_5H_4N$	44
(45e)*	PhSSPh	SOPh	31

* Prepared from (42) using 1.1eq tBuLi

The reaction is directly analogous to the conversion of **(9)** to **(19a)** in the formamidine series, however, in contrast to the products obtained *via* electrophilic substitution of **(18)**, the masked ketone functionality at C-3 of **(42)** could be released by mild acid hydrolysis using aqueous methanolic oxalic acid,[152] to give ketone **(43)** in 62% yield. This ketone was also available from ketal **(41)** using identical hydrolysis conditions. It is noteworthy that both of these hydrolysis reactions are chemoselective, liberating the ketone at C-3 in each case and leaving the acid-sensitive Boc group[78] untouched.

These results augered well for the successful utilization of the organolithium intermediate **(44)**, produced during the conversion of **(41)** to **(42)**, as a synthetic equivalent of a 3-pyrrolidinone C-2 enolate, and an investigation into the reaction of **(44)** with electrophiles was imperative (Scheme 28). The organolithium reagent **(44)** could be generated either from ketal **(41)** or from enol ether **(42)** and this parallels the preparation of **(18)** in the formamidine series (see Scheme 14, Section 1.1). In contrast to the formamidine-based reagent **(18)**, the Boc-protected alkenyllithium **(44)** did not react with alkyl halides, including iodomethane, and varying quantities of enol ether **(42)** were recovered from these reactions. However, organolithium **(44)** did react with aldehydes to give adducts **(45a-d)** in 40-44% yields after purification by chromatography (Table 2). Although the reactivity of **(44)** was independent of the precursor used (i.e. **(41)** or **(42)**), it was generally more convenient to start with ketal **(41)**, and the overall yields for the conversion of **(41)** to adducts **(45)** using this one-pot procedure were somewhat higher than those recorded using the alternative two-pot procedure.

Organolithium **(44)** was also reactive towards diphenyl disulphide as the electrophilic component. In this case, **(44)** was generated from **(42)** and a solution of diphenyl disulphide in THF was added dropwise at -78°C before the



OMe
Li
N
Boc
(44)
PhSSPh
OMe
SPh
N
Boc
(46)
PhSSPh
OMe
S+
Ph
SPh
N
Boc
(47)
H2O
OMe
S+
Ph
O-
N
Boc
(45e)

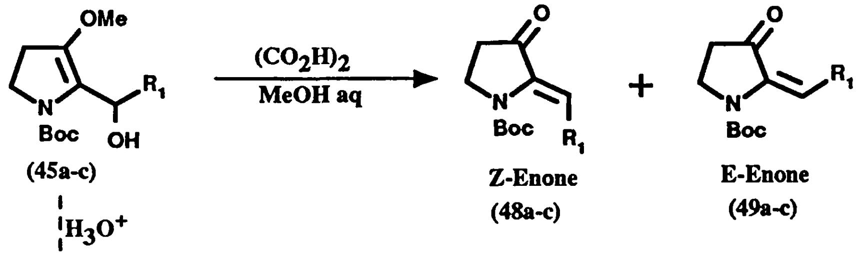
Scheme 29

reaction mixture was allowed to warm to ambient temperature and then quenched. Several unidentified minor products were produced in this reaction, but the major product was not the expected vinyl sulphide, but the crystalline vinyl sulphoxide **(45e)** (Table 2). It is not clear how this product arises. One possibility is that the initially formed vinyl sulphide **(46)** reacts with another molecule of diphenyl disulphide giving rise to vinyl sulphonium salt **(47)**, which undergoes hydrolysis on work-up to give **(45e)** (Scheme 29). The sulphur atom of putative intermediate **(46)** may exhibit enhanced nucleophilicity, as a result of the increased π-electron density at C-2 due to the methoxy group.

Although the aldehyde adducts **(45a-c)** were isolated cleanly when purified by rapid silica gel chromatography, these compounds were particularly acid-sensitive. Indeed, attempts to run the ^1H nmr spectra of these adducts in deuteriochloroform were thwarted by the immediate decomposition of the samples upon dissolution, presumably as a result of the acid present in the solvent. Dimethyl sulphoxide-d_6 was a suitable solvent for the ^1H nmr spectroscopic analysis of these adducts. Interestingly, the pyridyl derivative **(45d)**, which contains a basic nitrogen centre, was stable in deuteriochloroform and was generally less sensitive than the analogues **(45a-c)**. Full characterization of adducts **(45a-c)** was precluded because of the sensitivity of these materials and, therefore, the direct hydrolysis of the enol ether moiety was attempted.

1.3.2 Hydrolysis of the Aldehyde Adducts - The Preparation of Enones

Upon exposure to the mild acid hydrolysis conditions employed for the conversion of **(42)** to **(43)** (see Scheme 27), the adducts **(45a-c)** underwent a rapid reaction, leading to the formation of enones **(48)** and **(49)** (Scheme 30, Table 3). The formal aldol adducts were not observed in these reactions and are



Scheme 30

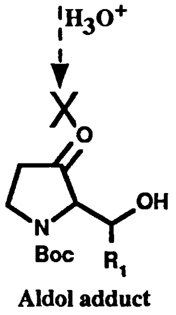
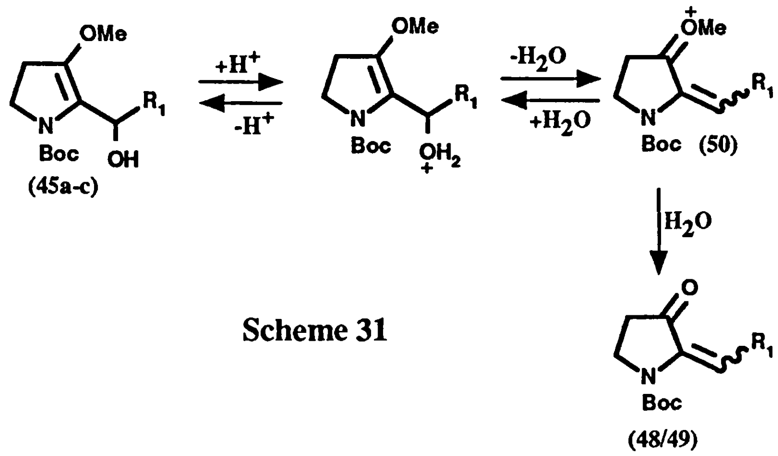
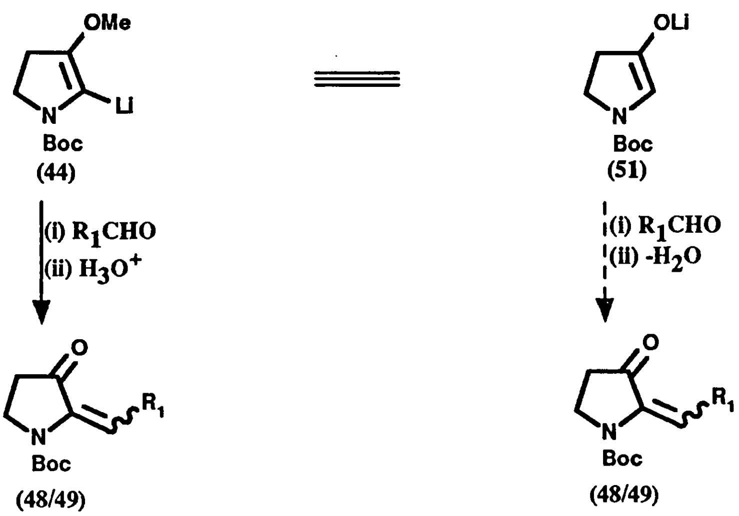


Table 3

Starting material	R_1 =	Products	
		Z-Enone (% yield)	E-Enone (% yield)
(45a)	Ph	-	(49a) (86)
(45b)	n-C_5H_{11}	(48b) (33)	(49b) (25)
(45c)	$CH(CH_3)_2$	(48c) (16)	(49c) (22)



Scheme 31

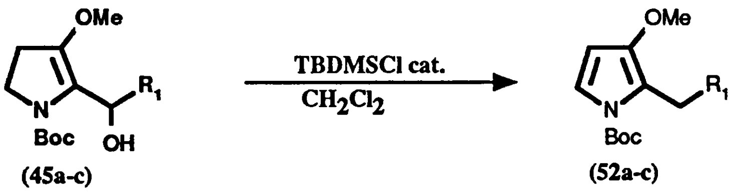


Scheme 32

probably not involved as intermediates in the formation of **(48)** and **(49)**, and there is considerable precedent for this type of cleavage in the literature. In general, acid hydrolysis of molecules containing δ-hydroxy or δ-alkoxy enol ether functionality results in the formation of α,β-unsaturated carbonyl compounds.[111c,110a-d,153]. A plausible mechanism for the reaction is outlined in Scheme 31. The enone that resulted from hydrolysis of **(45a)** was isolated as a crystalline solid and as a single geometrical isomer, tentatively assigned as the E-isomer **(49a)** based on the minimization of steric interactions in the transition state leading to oxonium ion **(50)**. Mixtures of Z- and E- isomers were obtained from hydrolysis of aldehyde adducts **(45b)** and **(45c)** and these isomers could be separated by careful chromatography on silica gel. The less polar isomers were identified as the Z-isomers **(48b)** and **(48c)** from the chemical shift of the olefinic protons in the ^{1}H nmr spectra of these products. These signals appeared 0.4-0.6 ppm downfield relative to the corresponding resonances for the more polar isomers, as expected for enone olefinic protons that lie in the anisotropic deshielding region of the carbonyl group.[154]

In general, the enones were somewhat unstable at room temperature, especially the Z-enones **(48b)** and **(48c)**. Since the formation of enones from the reaction of cyclic ketone enolates with aldehydes is a facile process,[83,155] it is clear that the acid hydrolysis of adducts **(45a-c)** establishes the synthetic equivalence of the organolithium reagent **(44)** to the 3-pyrrolidinone C-2 enolate **(51)**, albeit in a somewhat limited sense (Scheme 32).

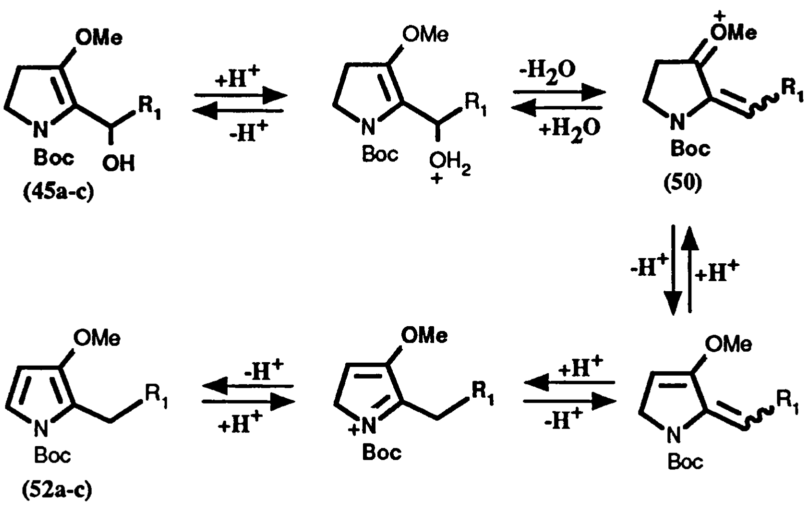
Not unexpectedly, the pyridyl derivative **(45d)** did not undergo hydrolysis at an appreciable rate when subjected to these mild hydrolysis conditions, and this behaviour is in keeping with the observed stability of this adduct in deuteriochloroform. Presumably, initial protonation of the basic pyridyl nitrogen atom retards the acid hydrolysis of **(45d)** which would then



(45a) R_1 = Ph
(45b) R_1 = n-C_5H_{11}
(45c) R_1 = $CH(CH_3)_2$

(52a) R_1 = Ph (50%)
(52b) R_1 = n-C_5H_{11} (71%)
(52c) R_1 = $CH(CH_3)_2$ (40%)

Scheme 33



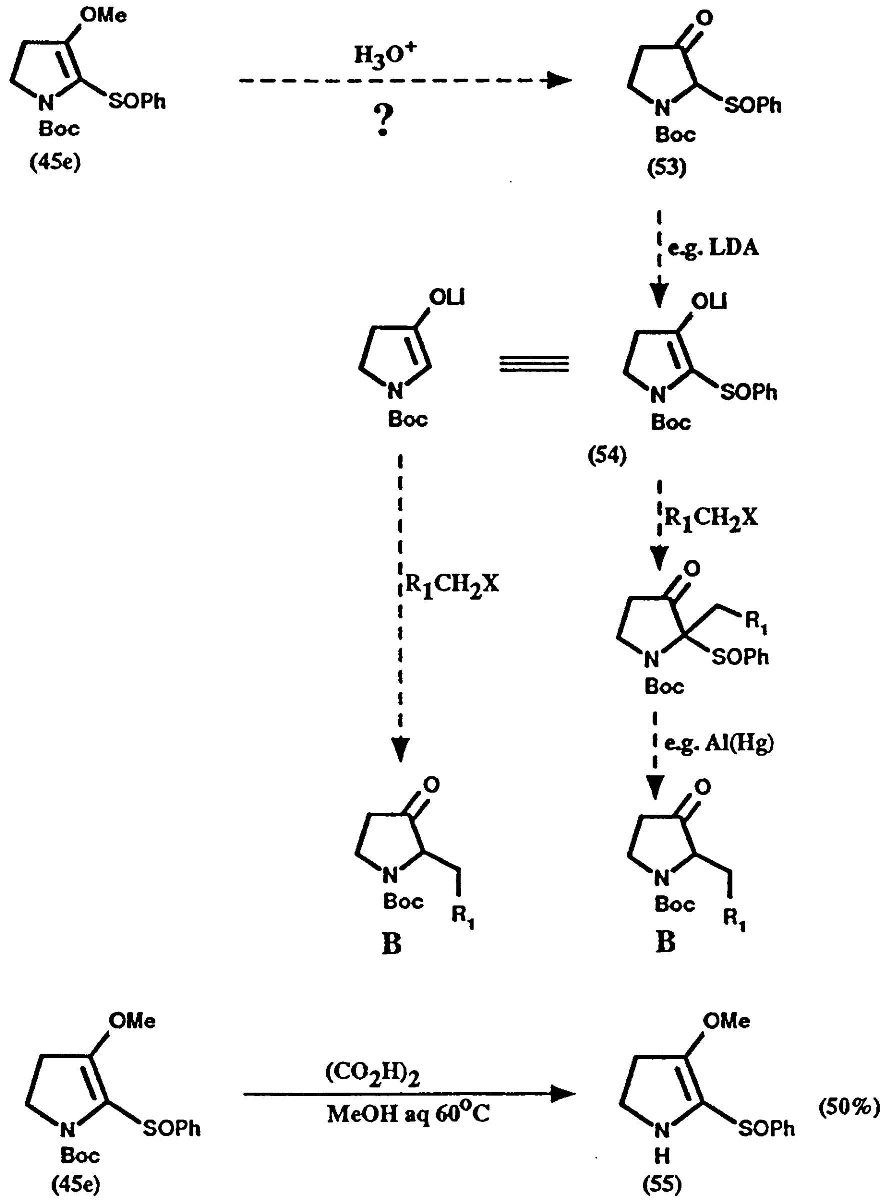
Scheme 34

necessitate the intermediacy of dicationic species. Slow decompositon of **(45d)** was observed upon extended exposure to aqueous methanolic oxalic acid, but no products could be isolated from this reaction.

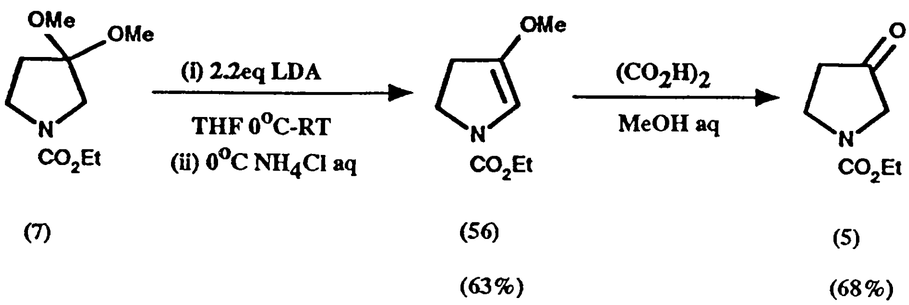
The characterization of enones **(48)/(49)** and the behaviour of **(45d)** may provide clues to the reasons for the labile nature of the aldehyde adducts **(19c)**, **(20d)**, **(27a/b)** obtained in the formamidine series (see Schemes 14, 17 and Table 1, Section 1.1). An analogous cleavage pathway for these products would result in the formation of molecules containing both an electrophilic enone unit and a nucleophilic amidine unit, and such incompatibility is likely to result in rapid deterioration.

1.3.3 Dehydration of the Aldehyde Adducts - The Preparation of Pyrroles

Interestingly, acid-catalyzed hydrolysis is not the only mode of fragmentation which the adducts **(45a-c)** display. Attempts to silylate the allylic hydroxyl group of **(45b)** led smoothly to the formation of the 2-pentyl-3-methoxy-pyrrole **(52b)**, and it was found subsequently that this dehydration could be effected most conveniently simply by treating a solution of the adduct **(45)** in dichloromethane with a catalytic quantity of *tert*-butyldimethylsilyl chloride (Scheme 33). Thus, 2-alkyl-3-methoxypyrroles **(52a-c)** were available from **(45a-c)** in reasonable yields. This represents a novel synthesis of these unusually substituted heterocycles, for which there are comparatively few preparative methods.[156] A reasonable mechanism for the reaction, again involving the generation of oxonium ion **(50)** (see Scheme 31), is proposed in Scheme 34. In the absence of an excess of water, a series of protonation/deprotonation equilibria lead ultimately to the observed pyrroles **(52)**.



Scheme 35



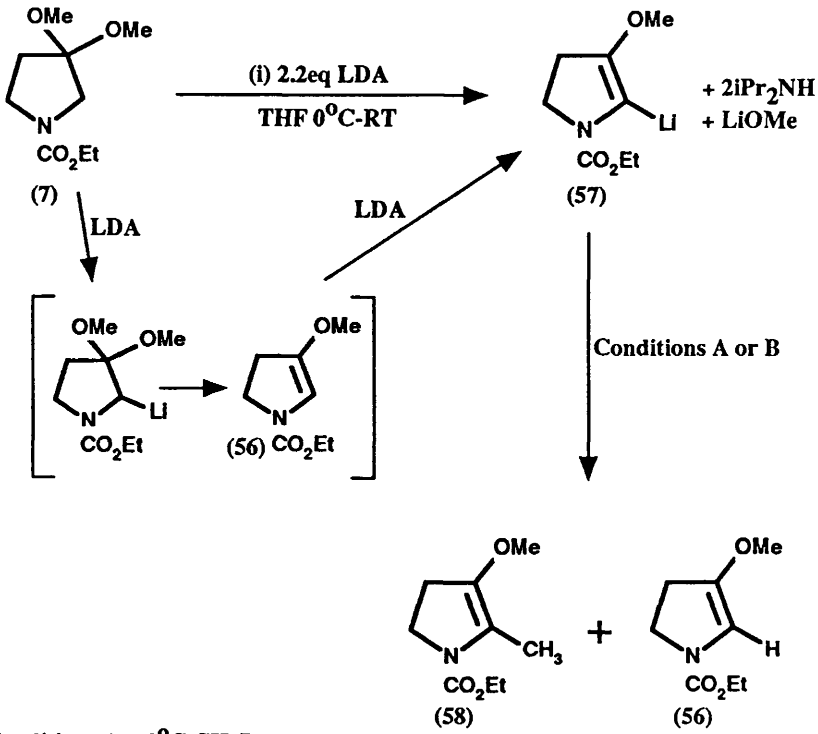
Scheme 36

1.3.4 Hydrolysis of the 2-Phenylsulphinyl-Substituted Adduct

The reactivity of the aldehyde adducts in acidic media was now well characterized, and the behaviour of sulphoxide **(45e)** towards treatment with aqueous acid was also examined. The expected product, β-keto sulphoxide **(53)**, could be regarded as a precursor to another potential C-2 enolate equivalent **(54)**, as shown in Scheme 35. Previous work has established that anions derived from β-keto sulphoxides[157] undergo reaction with electrophiles[158] to provide the α-substituted products, and that the sulphoxide residue is amenable to subsequent reductive removal.[159] However, when the sulphoxide **(45e)** was exposed to aqueous methanolic oxalic acid at room temperature, the enol ether moiety remained intact, and when the reaction mixture was warmed to 60°C, the Boc residue was cleaved selectively and the crystalline enamine **(55)** was isolated in 50% yield.

1.3.5 The N*-Ethoxycarbonyl Directed Metalation-Elimination-Metalation Reaction - Preparation and Electrophilic Substitution of a β-Lithiated Enol Ether*

The use of the Boc-protected organolithium reagent **(44)** as an enolate equivalent is severely limited since all attempts to alkylate this species using a variety of solvents and additives met with failure. In an attempt to overcome this problem, an alternative enol ether derivative was considered. The *N*-ethoxycarbonyl-protected ketal **(7)** (see Scheme 8, Section 1.1) was found to undergo the metalation-elimination-metalation sequence using the conditions shown in Scheme 36. In this case, ketal **(7)** was found to be incompatible with alkyllithium bases, presumably as a result of nucleophilic attack of the less sterically-demanding carbamate group.[142] However, the elimination reaction could be carried out efficiently using LDA rather than



Conditions A = 0^oC CH_3I

Conditions B = (i) $^-78^oC$
(ii) 1-2eq nBuLi
$^-78^oC$-RT
(iii) 0^oC CH_3I

Product ratio (58) : (56)

Conditions A ; 1 : 1

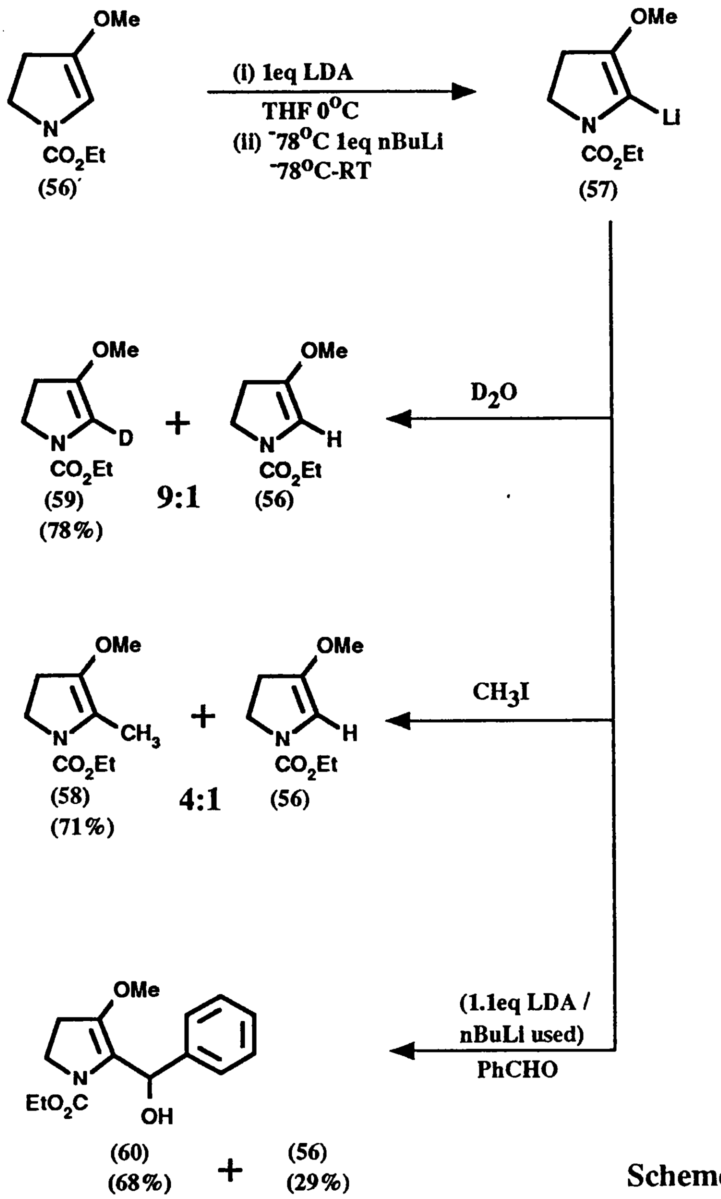
Conditions B ; 2.5 : 1

Scheme 37

tert-butyllithium as the base, and enol ether **(56)** was isolated in 63% yield after protic work-up. The hydrolysis of enol ether **(56)** using acidic hydrolysis conditions proceeded uneventfully to give ketone **(5)** in 68% yield

It is not clear whether *N*-ethoxycarbonyl-*N,N*-dialkylamines, in general, offer sufficiently high acidity for efficient α-lithiation *via* deprotonation by LDA under these conditions, or if the elimination reaction proceeds *via* the $ElcB_R$ mechanism,[160] wherein small equilibrium concentrations of α-lithiated species are generated which undergo β-elimination. Lithium dialkylamide bases have been found to be ineffective[150] for the α-lithiation of the simple Boc-protected derivatives described by Beak and Lee,[151] however, this may be a result of sterically disfavoured reagent approach, since we have found that the Boc-protected ketal **(41)** does not undergo the elimination reaction with LDA. The efficient α- and β-lithiation of non-enolizable ketones with lithium dialkylamide bases has recently been reported.[161]

The alkylation of the organolithium intermediate **(57)**, generated *en route* to (56), was next investigated. Unlike the Boc-protcted derivative (44), alkylation of **(57)** with iodomethane proceeded to give a 1:1 mixture of **(56)** and the 2-methyl derivative (58) (Conditions A, Scheme 37). Surprisingly, the attempted separation of these two products by chromatography on silica gel resulted in the decompositon of (58), however, the crude product mixtures isolated by standard extractive procedures were clean, and analysis by ^1H nmr spectroscopy was straightforward. The reason for the incomplete alkylation of **(57)** was unclear at this stage, but previous studies have shown that incomplete alkylation or deuteration of organolithium species generated by deprotonation with lithium dialkylamide bases can be attributed to the "secondary amine effect", where the organolithium remains associated with the dialkylamine

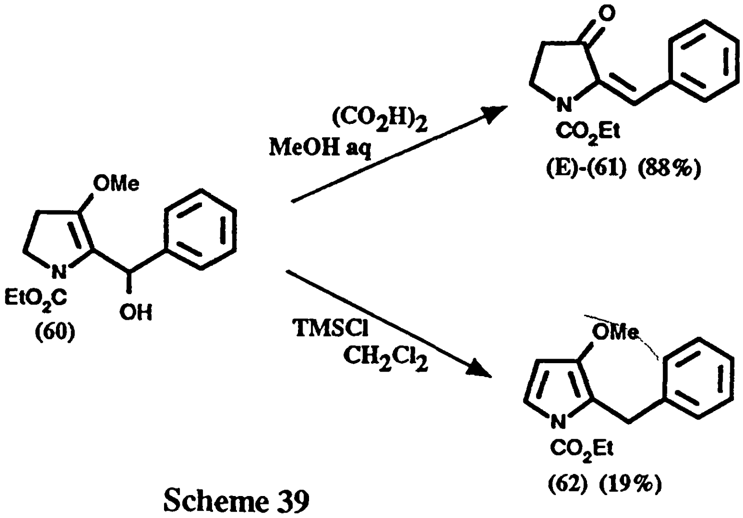


OMe
N
CO2Et
(56)
(i) 1eq LDA
THF 0°C
(ii) -78°C 1eq nBuLi
-78°C-RT
OMe
Li
N
CO2Et
(57)
D2O
OMe
D
N
CO2Et
(59)
(78%)
9:1
OMe
H
N
CO2Et
(56)
CH3I
OMe
CH3
N
CO2Et
(58)
(71%)
4:1
OMe
H
N
CO2Et
(56)
(1.1eq LDA /
nBuLi used)
PhCHO
OMe
N
EtO2C
OH
(60)
(68%)
(56)
(29%)

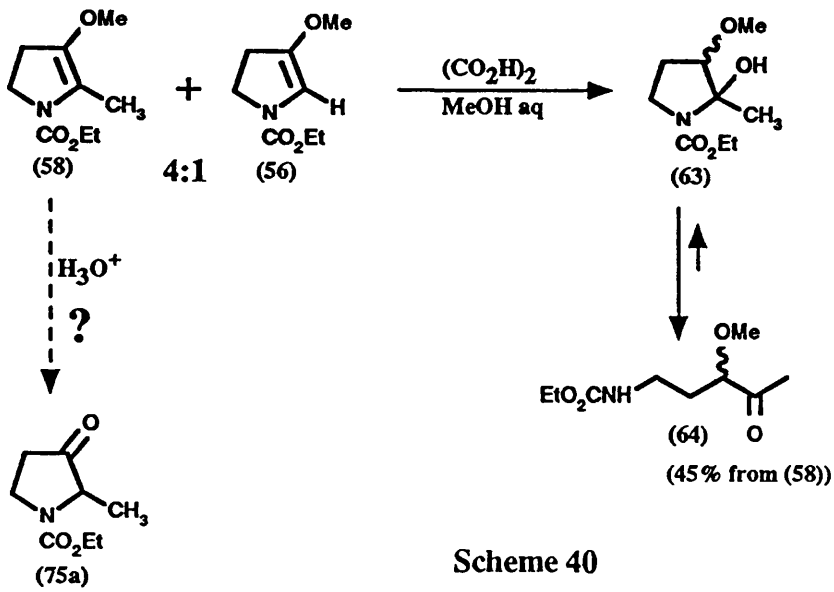
Scheme 38

produced in the deprotonation step.[162] The degree of aggregation of such organolithium entities, or organolithium-dialkylamine complexes, may also dictate the reactivity of these species in solution. The removal of the dialkylamine protic source from the reaction medium by the addition of *n*-butyllithium has been shown to augment the efficiency of the subsequent alkylation[163] or deuteration[164] of certain organolithium derivatives. In accordance with these findings, we observed that the generation of **(57)** from **(7)** using LDA (2.2 equivalents), followed by the dropwise addition of *n*-butyllithium (1-2 equivalents) at -78°C and then alkylation at 0°C with iodomethane, resulted in an increase in the ratio of **(58)**:**(56)** to 2.5:1 (Conditions B, Scheme 37). Again, the crude product mixture isolated from this reaction was reasonably clean, suggesting that the deprotonation of diisopropylamine by *n*-butyllithium competed favourably with nucleophilic attack of the carbamate group under these kinetic conditions. Thus, it appeared that the diisopropylamine generated in the formation of **(57)** did indeed exert a detrimental effect on the subsequent methylation of this species, although the incomplete deprotonation of (56) could not be ruled out.

In order to prevent any complications associated with the presence of one equivalent of lithium methoxide and up to two equivalents of diisopropylamine that are formed during the conversion of **(7)** to **(57)**, the deuteration of **(57)** as generated from isolated enol ether **(56)** was examined, as an indication of the efficiency of this lithiation process. When enol ether **(56)** was treated with LDA (1 equivalent) at 0°C followed by *n*-butyllithium (1 equivalent) at -78°C, and the reaction mixture was quenched with D_2O, a 9:1 mixture of 2-deuterio:2-protio derivatives **(59)**:**(56)** was isolated in high yield (Scheme 38). Thus, organolithium **(57)** was generated efficiently by deprotonation of (56) under these conditions.



Scheme 39

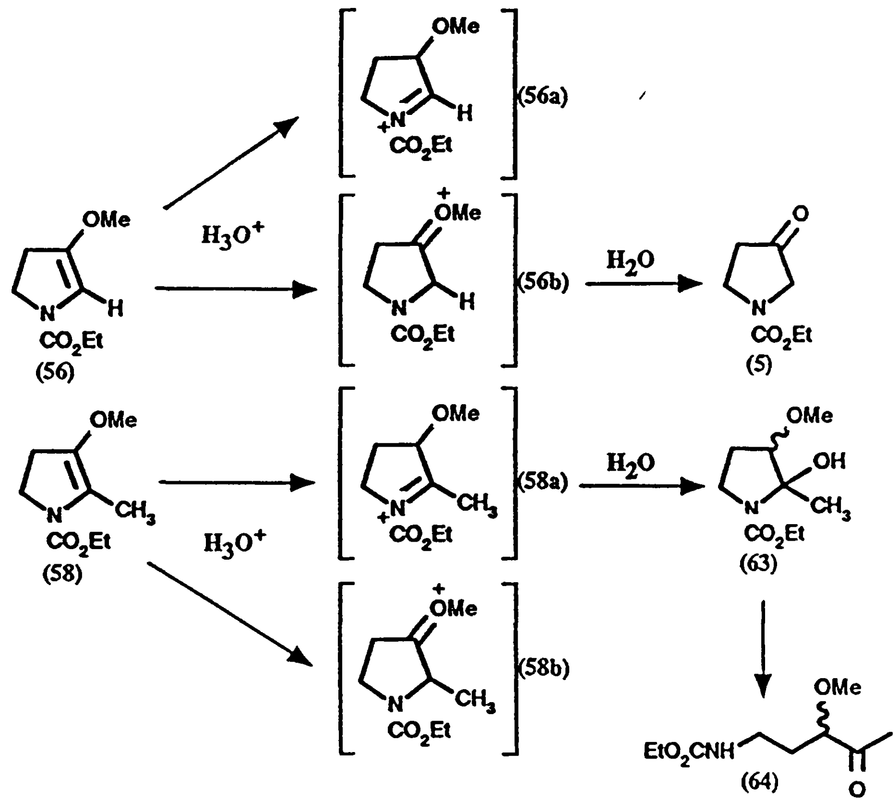


Scheme 40

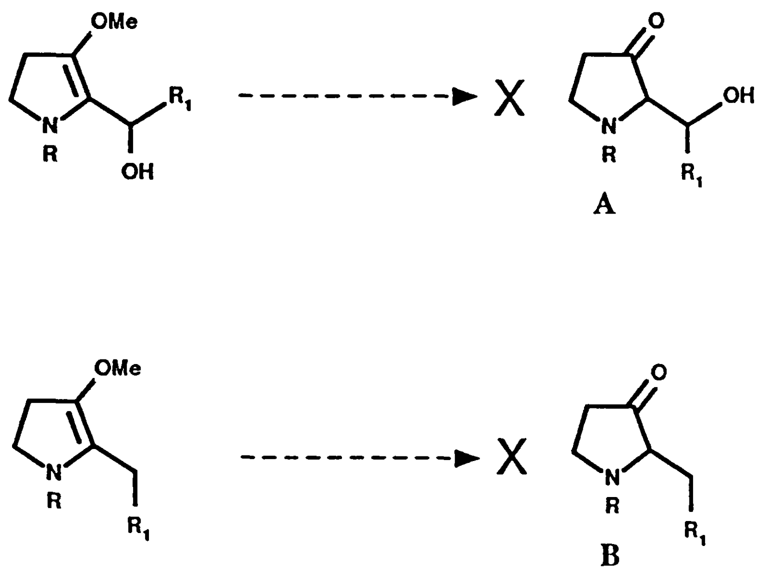
The corresponding methylation of (57), prepared from (56) using this lithiation protocol, proceeded to give a 4:1 mixture of 2-methyl:2-protio derivatives (58):(56), corresponding to a 71% yield of (58). That the observed ratio of (58):(56) obtained from this reaction does not reflect the observed ratio of 2-deuterio:2-protio derivatives obtained in the deuteration experiment, may attest to the reluctance of alkenyllithium species of this type to undergo alkylations in general, as evidenced by the failure of (57) to react with other allyl, benzyl or alkyl halides. Reaction of (57) with benzaldehyde furnished the expected adduct (60) in 68% yield (96% accounting for recovered (56)). The higher yield observed in this reaction compared to the addition of the Boc-protected organolithium (44) to aldehydes (see Scheme 28, Table 2) is probably due to the milder conditions employed for the generation of (57). Adduct (60) exhibited a similar pattern of reactivity towards acidic reagents to that of the Boc-protected adducts (45a-c), giving a crystalline enone (61) in 88% yield upon aqueous acidic hydrolysis, and a pyrrole (62) in 19% yield when treated with a catalytic quantity of trimethylsilyl chloride (Scheme 39).

1.3.6 Hydrolysis of the 2-Methyl-Substituted Adduct

The 4:1 mixture of 2-methyl:2-protio enol ether derivatives, obtained from methylation of (57), was also subjected to acidic hydrolysis as shown in Scheme 40. A number of unidentified products were produced in this reaction, but the major product, isolated in 45% yield (based on (58)), was the *N*-ethoxycarbonyl-γ-amino ketone (64) and not the expected 2-methyl-substituted 3-pyrrolidinone (75a) (see Section 2.2). The presence of a ketonic resonance at δ 210.7 in the ^{13}C nmr spectrum of (64), confirmed that the open chain form predominated over the cyclic *O,N*-hemiketal isomer (63), although the carbonyl stretching absorbance of the ketone was not resolved from that of the carbamate in the IR spectrum of this product. *N*-Alkoxycarbonyl-γ-amino



Scheme 41



R = CO_2Et, Boc

Scheme 42

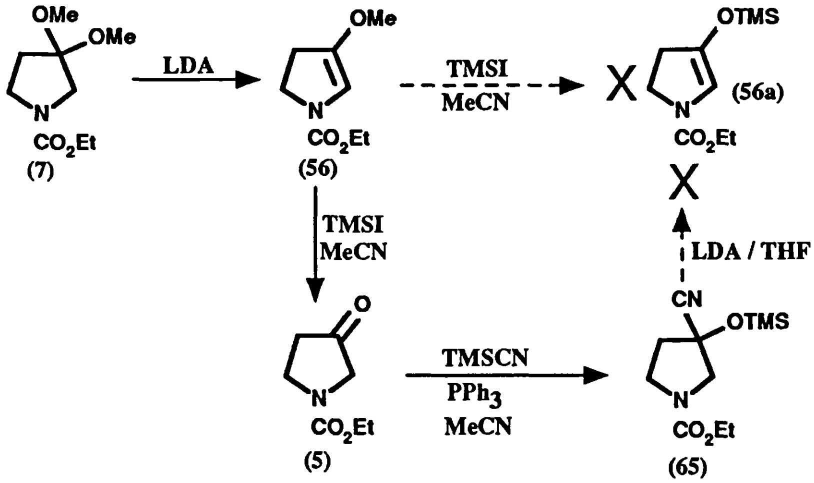
ketones related to **(64)** have previously been prepared by Goodman and coworkers *via* 4-oxopentyl isocyanates.[(165)]

The formation of **(64)** probably proceeds *via* the cyclic isomer **(63)**, which is clearly the hydration product of **(58)**, arising from protonation at C-3; i.e. **(58)** has undergone acid hydrolysis as an enamine rather than as an enol ether. This remarkable behaviour contrasts starkly with that of the unsubstituted compound **(56)**, which undergoes hydrolysis as an ethol ether under idential conditions, leading smoothly to ketone **(5)** (see Scheme 36). The switching of the hydrolysis pathway upon the introduction of an alkyl substituent at C-2 in this system is quite striking, and may reflect the predominance of the proposed intermediates, oxonium ion **(56b)** and acyliminium ion **(58a)**, over the alternatives, acyliminium ion **(56a)** and oxonium ion **(58b)**, respectively (Scheme 41). Presumably, the acyliminium species is subject to hyperconjugative stabilization by the C-2 alkyl group. There may also be a steric effect operating between the C-2 methyl substituent and the C-3 methoxy group in **(58)**.

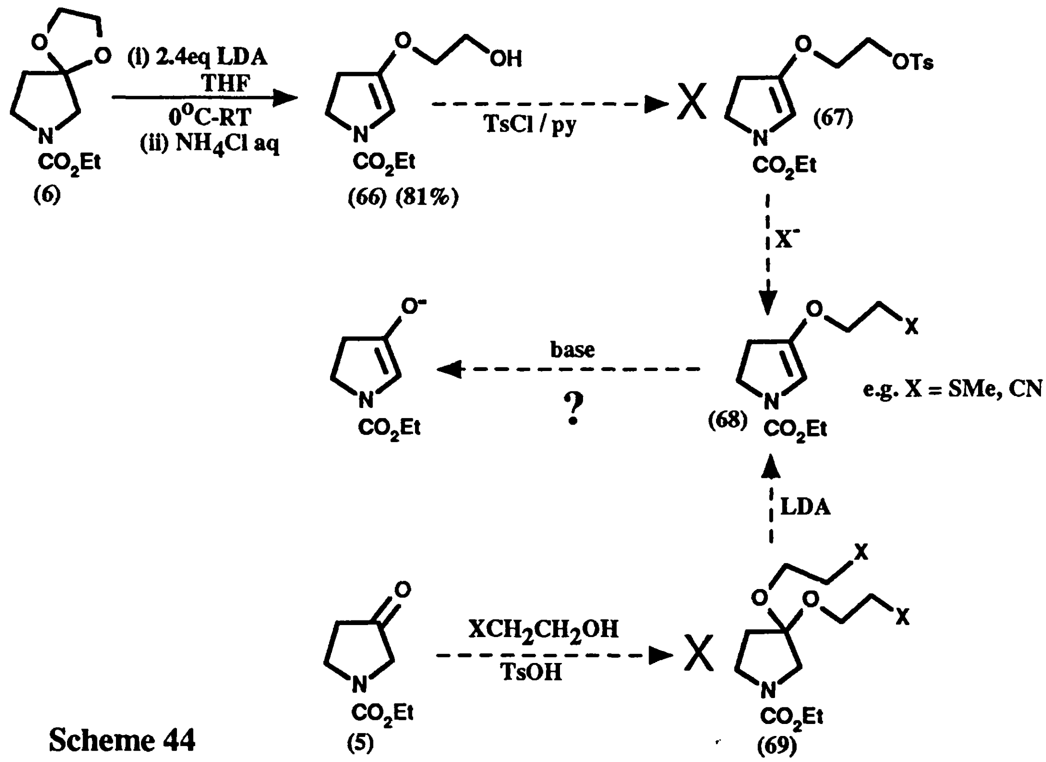
The enamine reactivity associated with **(58)** may explain the observed decomposition of this material upon attempted chromatography on silica gel, and also suggests a possible reason for the instability of the 2-alkylated formamidine derivatives (see Scheme 14 and Table 1, Section 1.1).

1.3.7 The Limitations of the Metalated Enol Ether Approach

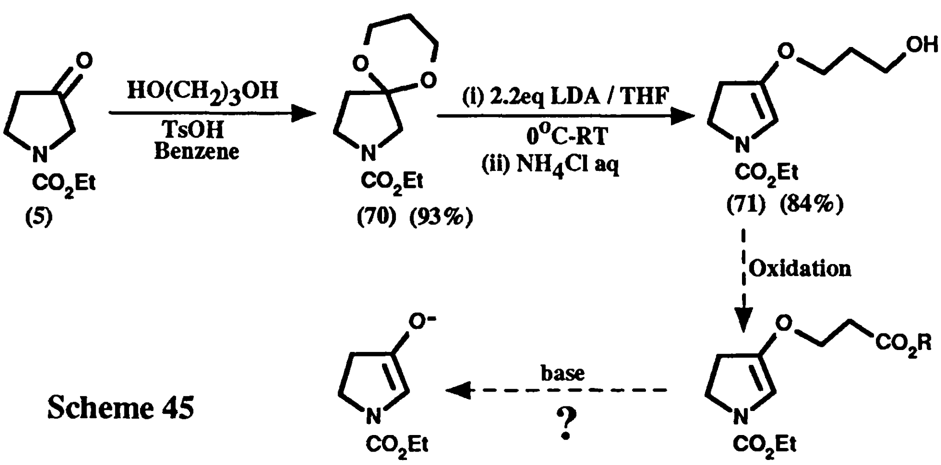
The general modes of reactivity displayed by the aldehyde adducts **(45a-c)** and **(60)**, and the alkylated derivative **(58)**, demonstrated that the organolithium reagents **(44)** and **(57)** could not be regarded as general C-2 enolate equivalents of 3-pyrrolidinones. Neither the formal aldol adducts A, nor



Scheme 43



Scheme 44



Scheme 45

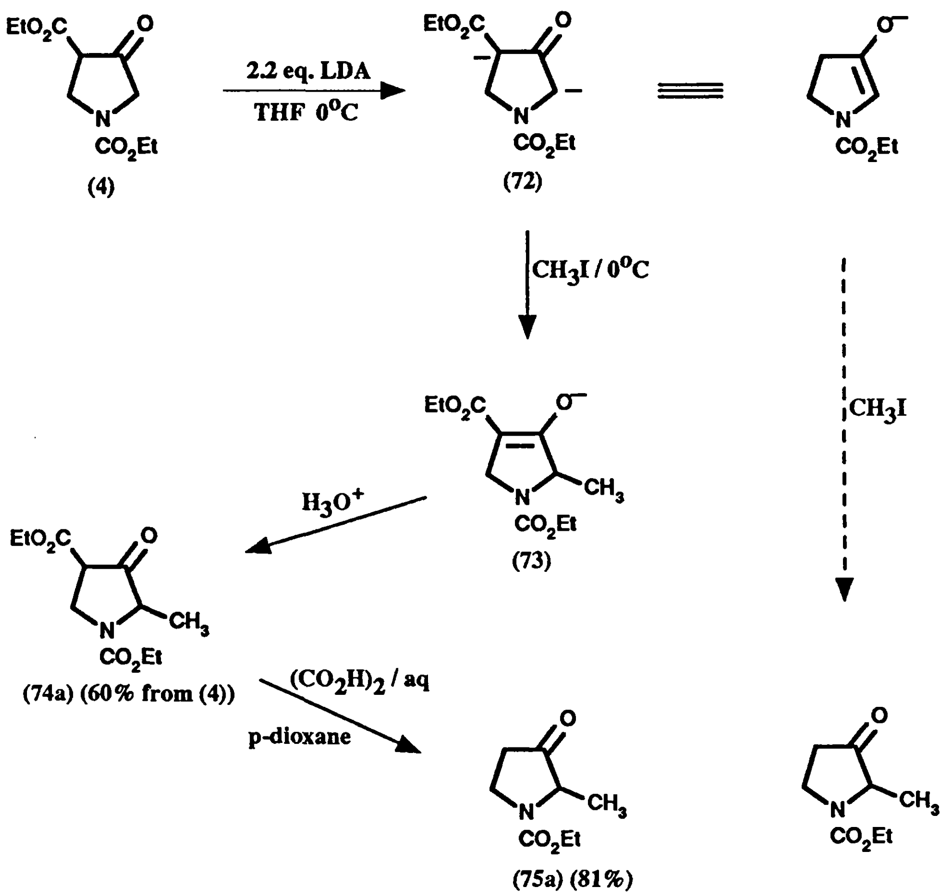
the C-2 alkylated pyrrolidinones B were available directly using this methodology (Scheme 42) (see Introduction, Section 3.1).

Some final efforts to exploit the LDA-induced elimination reaction and develop alternative precursors to the C-2 enolate are summarized in Scheme 43-45.

Trimethylsilyl enol ethers have been used as enolate equivalents in Lewis-acid catalyzed aldol-type reactions(166) and also as enolate precursors.(167,181) The preparation of the regiospecific trimethysilyl enol ether **(56a)** from methyl enol ether **(56)** using iodotrimethylsilane was attempted but none of the desired product could be isolated and invariably ketone **(5)** was produced (Scheme 43). The iodotrimethylsilane-mediated cleavage of methyl enol ethers to give the corresponding carbonyl compounds is a facile reaction(140), however, to the best of our knowledge trimethylsilyl enol ethers have not been isolated from this reaction, although the analogous conversion of a ketene-*O*-methyl,*S*-acetal to a ketene-*O*-silyl,*S*-acetal has been reported.(168) Attempts to prepare **(56a)** *via* the *O*-trimethylsilyl cyanohydrin **(65)** derived from ketone **(5)**(169) also failed.

Application of the elimination reaction to cyclic ketals **(6)** and **(70)** afforded the alcohols **(66)** and **(71)** in 81% and 84% yields respectively (Schemes 44 and 45). These products suffered complete reversion to their respective cyclic acetal precursors upon dissolution in deuteriochloroform, presumably as a result of acid-catalyzed cyclization in this solvent. Tosylation of **(66)** was attempted with a view to subsequent nucleophilic displacement to provide enol ethers of type **(68)**, which, in principle, could provide access to the desired C-2 enolates *via* a β-elimination process.(170) Unfortunately, **(67)** could not be isolated from this reaction which resulted in a substantial degree of decompositon. An alternative route to derivatives of **(68)** (X = SMe and X = $SiMe_3$[171]) *via* LDA-induced elimination of alkoxide from the *bis*-methylthioethyl and *bis*-trimethylsilylethyl ketals **(69)**, was precluded when the ketalisation of **(5)** with the requisite alcohols failed. The β-elimination of an oxidation product of **(71)** was also considered as a means of gaining access to the C-2 enolate, but all efforts to oxidize this alcohol proved unsatisfactory.

At this stage, our attention turned completely to a different approach to the regiospecific C-2 substitution of 3-pyrrolidinones. This approach was based on the use of a β-keto ester dianion as an enolate equivalent, and constitutes a pivotal element of the chemistry discussed in the remainder of this thesis.



EtO_2C
O
N
CO_2Et
(4)
2.2 eq. LDA
THF 0^oC
(72)
O^-
CH_3I / 0^oC
CH_3I
(73)
CH_3
H_3O^+
(74a) (60% from (4))
$(CO_2H)_2$ / aq
p-dioxane
(75a) (81%)

Scheme 46

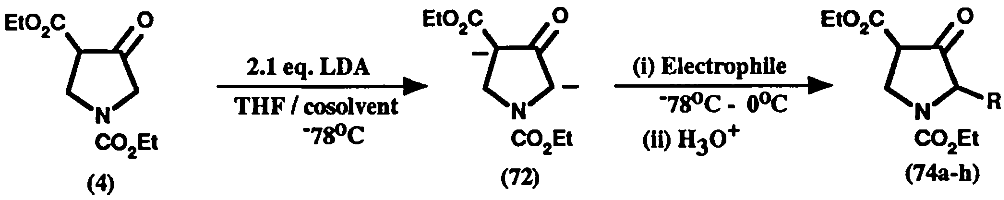
2 *Heterocyclic β-Keto Ester Dianions as Regiospecific Enolate Equivalents*

2.1 *Initial Studies*

The propensity of dianions of β-keto esters[172] to undergo alkylation,[173] acylation,[174] Michael addition[175] and aldol-type condensation,[176] leading to a γ-substitution products, provides a useful method for carbon-carbon bond formation. In the Introduction (Section 3.7) we proposed that this type of chemistry might be applied to the synthesis of 2-substituted-3-pyrrolidinones using the dianion derived from heterocyclic β-keto ester. This prompted a search for reaction conditions suitable for the efficient double deprotonation of the known β-keto ester **(4)**,[122] which was prepared *via* a Dieckmann cyclization as an intermediate in the synthesis of ketone **(5)** (see Scheme 6, Section 1.1).

Initial experiments were performed using LDA (2.2 equivalents) as the base in THF at 0°C according to the procedure of Huckin and Weiler.[173f] When a solution of β-keto ester **(4)** in THF was added to the solution of LDA, an orange precipitate was produced which was stirred at 0°C for 20 minutes. The addition of iodomethane (1.3 equivalents) caused complete dissolution of the precipitate to give an orange solution, and the formation of a new product was observed which was isolated using standard procedures and characterized as the 2-methyl adduct **(74a)** (Scheme 46). This product was obtained in 60% yield.

Thus, it appeared that treatment of **(4)** with two equivalents of LDA effectively generated the dianion **(72)**, which exhibited low solubility in THF at 0°C, but which reacted with iodomethane despite this to give, presumably, soluble monoanion **(73)** before the reaction was quenched to provide the



Scheme 47

Cosolvent	Electrophile	Product	R =	Yield %
HMPA	CH_3I	(74a)	CH_3	62
DMPU	CH_3I	(74a)	CH_3	73
HMPA	n-$C_5H_{11}Br$	(74b)	n-C_5H_{11}	45
DMPU	n-$C_5H_{11}Br$	(74b)	n-C_5H_{11}	56
HMPA	$PhCH_2Br$	(74c)	CH_2Ph	51
HMPA	$H_2C{=}CHCH_2Br$	(74d)	$CH_2CH{=}CH_2$	54
DMPU	$H_2C{=}CHCH_2Br$	(74d)	$CH_2CH{=}CH_2$	56
HMPA	$PhCH_2O(CH_2)_3I$	(74e)	$(CH_2)_3OCH_2Ph$	70
DMPU	$(CH_3)_2CHCHO$	(74f)	$CH(OH)CH(CH_3)_2$	88
DMPU	n-$C_5H_{11}CHO$	(74g)	$CH(OH)C_5H_{11}$	71
DMPU	PhCHO	(74h)	CH(OH)Ph	87

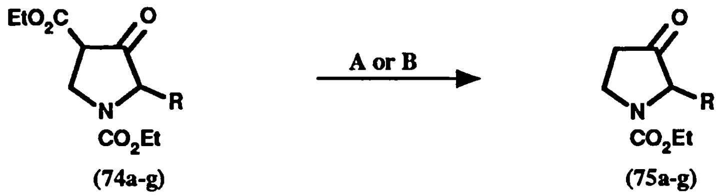
Table 4

product **(74a)**. This was a pleasing result since substitution of the pyrrolidinone nucleus at C-2 had been achieved, and the desired 2-methyl-3-pyrrolidinone **(75a)** was available directly from **(74a)** using a simple deethoxycarbonylation reaction. This transformation was accomplished by conventional acid hydrolysis and decarboxylation using aqueous oxalic acid in dioxane at reflux; a modification of the procedure described by Bühler and Viscontini for the deethoxycarbonylation of **(4)**.[114] The expected product **(75a)** was obtained in 81% yield from **(74a)**.

Clearly, the dianion **(72)** had served as a synthetic equivalent of the 3-pyrrolidinone C-2 enolate in this case, and the two-step procedure for the preparation of **(75a)** represented the first successful solution to the general problem of regioselective enolization of 3-pyrrolidinones. Studies directed at the extension of this methodology for the synthesis of a variety of 2-substituted-3-pyrrolidinones are described below.

2.2 The Synthesis of 2-Substituted-3-Pyrrolidinones.

In order to evaluate the generality of the overall process and assess the status of dianion **(72)** as a practicable enolate equivalent, it was important to determine the range of electrophiles with which this dianion would react. In addition to extending the procedure to the synthesis of other C-2 alkyl adducts, the preparation of the elusive C-2 aldol adducts *via* the aldol-type condensation of **(72)** with aldehydes was of interest. A study of the reactivity of dianion **(72)** towards alkyl halides and aldehydes was undertaken, and during the course of these experiments the poor solubility of this dianion in THF was overcome by the addition of a small quantity of HMPA as cosolvent, which solubilized the dianion providing a clear red solution. When generated in this manner, dianion **(72)** was found to be reactive towards alkyl halides at -78°C, in contrast to the



General Procedure A: $(CO_2H)_2$ aq / p-dioxane Δ
General Procedure B: NaCl / wet DMSO / 130-135°C

Scheme 48

Starting material	General Procedure	Product	R =	Yield %	Entry
74a	A	75a	CH_3	81	1
74b	A	75b	n-C_5H_{11}	77	2
74b	B	75 b	n-C_5H_{11}	76	3
74c	A	75c	CH_2Ph	88	4
74d	A	75d*	$CH_2C{=}CH_2$	67	5
74e	A	75e	$(CH_2)_3OCH_2Ph$	89	6
74f	B	75f	$CH(OH)CH(CH_3)_2$	91	7
74g	A	75g	$CH(OH)C_5H_{11}$	55	8
74g	B	75g	$CH(OH)C_5H_{11}$	77	9
74h	A or B	75h	CH(OH)Ph	see text	10

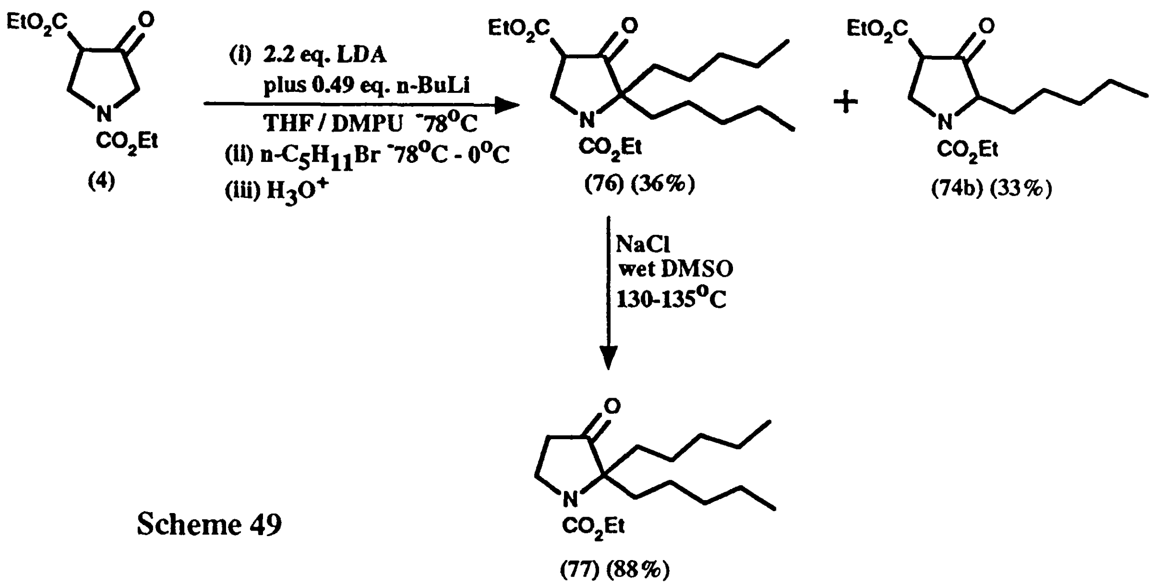
*see ref. 178

Table 5

observations of Huckin and Weiler for the alkylation of dianions derived from simple β-keto esters.[173f]

Further experimentation revealed that the highly toxic additive HMPA could be replaced by the cyclic urea DMPU, which was first introduced as a cosolvent for carbanion reactions by Seebach.[177] A slightly larger quantity of DMPU than HMPA was required to maintain complete solubility of the dianion at -78°C, but the alkylations proceeded with equal, or with greater efficiency in this solvent system, and the aldol-type reactions of **(72)** with aldehydes were particularly high-yielding under these conditions. The results of these experiments are summarized in Scheme 47 and Table 4. The adducts **(74a-h)** were isolated in good yields as mixtures of diastereoisomers and keto-enol tautomers. The presence of variable proportions of the enol tautomers was indicated by the signal for the enolic proton at around δ 10.1 in the ^{1}H nmr spectra of the adducts **(74)**. These spectra were highly complex and the adducts were not fully characterized at this stage.

Facile deethoxycarbonylation of the adducts was accomplished in one of two ways (Scheme 48, Table 5). The 2-alkylated adducts **(74a-e)** underwent smooth hydrolysis and decarboxylation when subjected to the acidic hydrolysis conditions (Method A) and the corresponding 2-alkyl-3-pyrrolidinones **(75a-e)** were obtained in good yields. Ketone **(75d)** has previously been synthesized by Kametani and coworkers using a highly selective Claisen rearrangement.[178] Lower yields were observed when this deethoxycarbonylation method was applied to the aldehyde adducts (e.g. entry 8, Table 5), however, efficient cleavage of the ethoxycarbonyl moiety from **(74f)** and **(74g)** could be effected using sodium chloride in wet dimethyl sulphoxide at 130-135°C (Method B), as described by Krapcho.[179] The aldol products **(75g)** and **(75h)** were obtained in high yields as colourless oils, homogeneous by TLC, and this procedure also



(4)
(i) 2.2 eq. LDA
plus 0.49 eq. n-BuLi
THF / DMPU -78°C
(ii) n-C5H11Br -78°C - 0°C
(iii) H3O+
(76) (36%)
+
(74b) (33%)
NaCl
wet DMSO
130-135°C
(77) (88%)

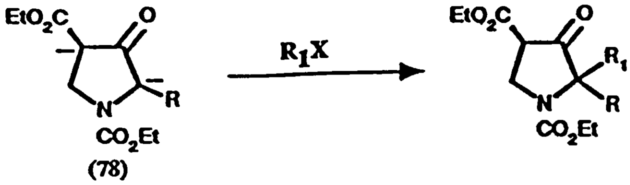
Scheme 49

worked well for the alkylated adducts (e.g. entry 3, Table 5).

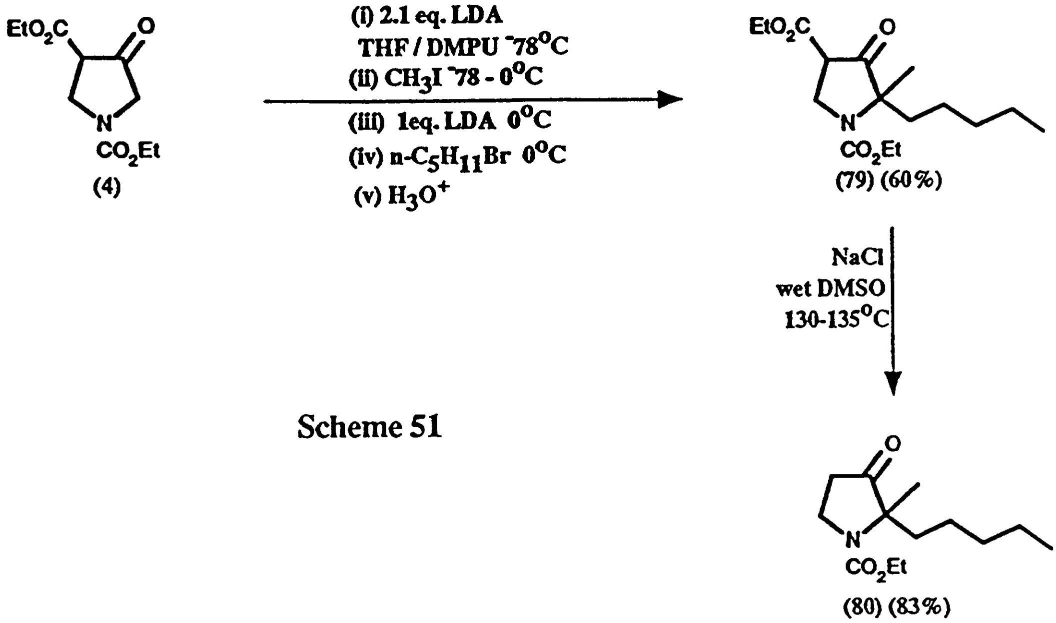
The benzaldehyde adduct **(74h)** exhibited aberrant behaviour when deethoxycarbonylation was carried out using either method and for reasons that are not clear, adduct **(74h)** was especially sensitive to retro-aldol fragmentation. The aldol product **(75h)** was formed, but only as an inseparable mixture (1-3:1 ratio by ^{1}H nmr) with *N*-ethoxycarbonyl-3-pyrrolidinone **(5)**. Recent studies have highlighted the idiosyncratic stereochemical course of aldol reactions involving benzaldehyde,[(180)] and the anomalous stereoselectivities observed in fluoride-promoted aldol reactions of silyl ketene acetals with benzaldehyde has been attributed to equilibration *via* retroaldol reaction,[(180)] a process which appears to be particularly prevalent in reactions involving "naked" aldol anions derived from aromatic aldehydes, especially electron-rich benzaldehydes.[(181)] The best ratio of **(75h)**:**(5)** obtained from deethoxycarbonylation of **(74h)** was 3:1 (Method A), and the aldol product present in this mixture consisted of a 3:2 mixture of diastereoisomers by ^{1}H nmr. The ratio of diastereoisomers present in aldols **(75f)** and **(75g)** could not be determined by ^{1}H nmr.

2.3 The Synthesis of 2,2-Disubstituted-3-Pyrrolidinones

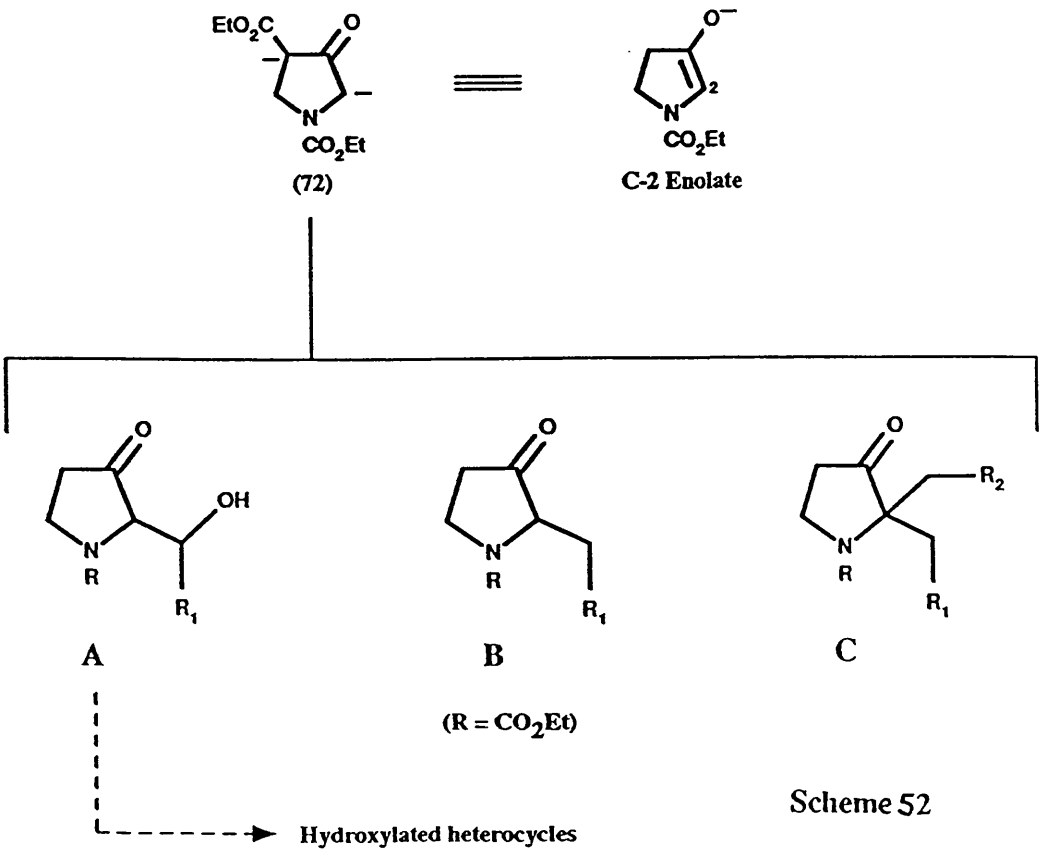
Having successfully gained access to the desired C-2 alkylation and aldolization products of 3-pyrrolidinones, a useful extension of this dianion-based methodology was realized, involving the introduction of a second C-2 substitutent. During an attempted preparation of the pentyl derivative **(74b)**, the inadvertent addition of a surplus of *n*-butyllithium resulted in the formation of a faster-moving product (by TLC) in addition to the expected product **(74b)**. This new product was isolated and characterized as the 2,2-dipentyl adduct **(76)** (Scheme 49). The yield of this material was 33% and the monoalkylated adduct **(74b)** was also obtained in 36% yield.



Scheme 50



Scheme 51

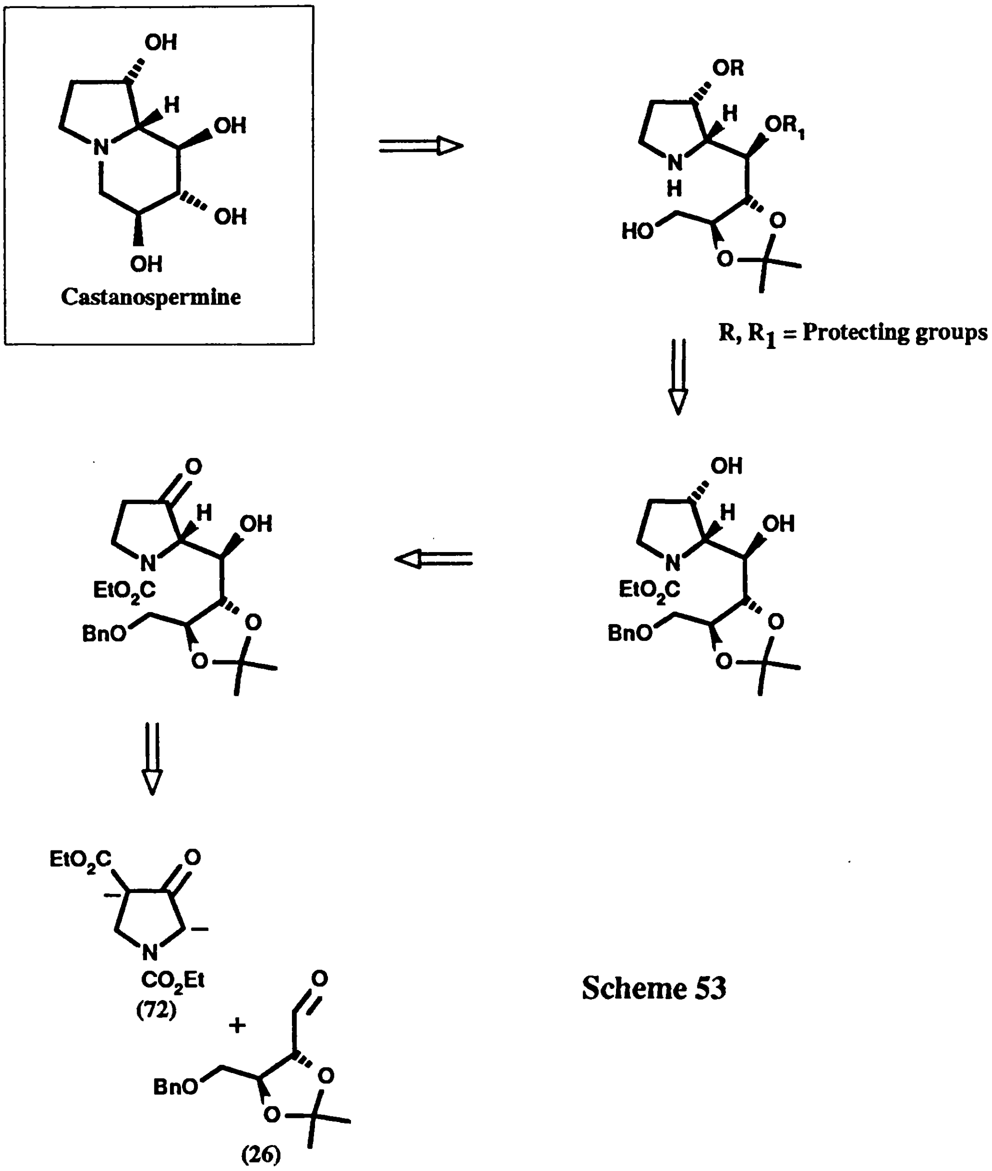


Scheme 52

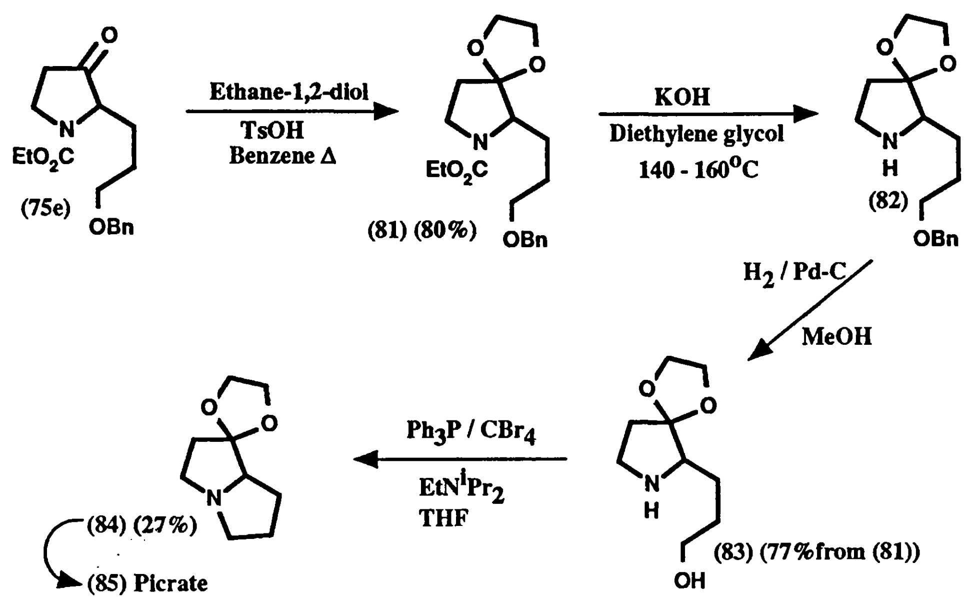
Deethoxycarbonylation of **(76)** gave the dialkylated 3-pyrrolidinone **(77)** in 88% yield. The formation of **(76)** suggested that the alkylation of a dianion which already contained a C-2 substituent was feasible[173f] (Scheme 50). The sequential introduction of two different alkyl groups at C-2 of β-keto ester **(4)** was accomplished by employing a one-pot procedure, exemplified by the sequence shown in Scheme 51. Alkylation of dianion **(72)** with iodomethane, followed by the addition of a further equivalent of LDA and then 1-bromopentane, gave the dialkylated adduct **(79)** in 60% overall yield. The second alkylation step was carried out at 0°C, in order to avoid the undesirable precipitation of solid materials, and the adduct **(79)** was converted to the 2,2-dialkyl-3-pyrrolidinone **(80)** in 83% yield.

2.4 The Scope of the Dianion-Based Methodology

The successful application of this dianion chemistry to the synthesis of a variety of 2-substituted-3-pyrrolidinones, including aldol adducts **A**, alkylated products **B**, and dialkylated derivatives **C**, establishes the dianion **(72)** as a general synthetic equivalent of a 3-pyrrolidinone C-2 enolate (Scheme 52). In this context, dianion **(72)** is vastly superior to the alternative organolithium reagents **(44)** and **(57)**, which function as enolate equivalents only in a very limited sense. Aldol-type chemistry involving dianion **(72)** offers great potential for the synthesis of hydroxylated heterocycles, *via* structural type A (Scheme 52), and opens the way for the implementation of the strategies outlined in the Introduction (Section 3.1). Our efforts to apply this methodology to the synthesis of the polyhydroxylated indolizidine, castanospermine, are discussed in the final section of this thesis.



Scheme 53



Scheme 54

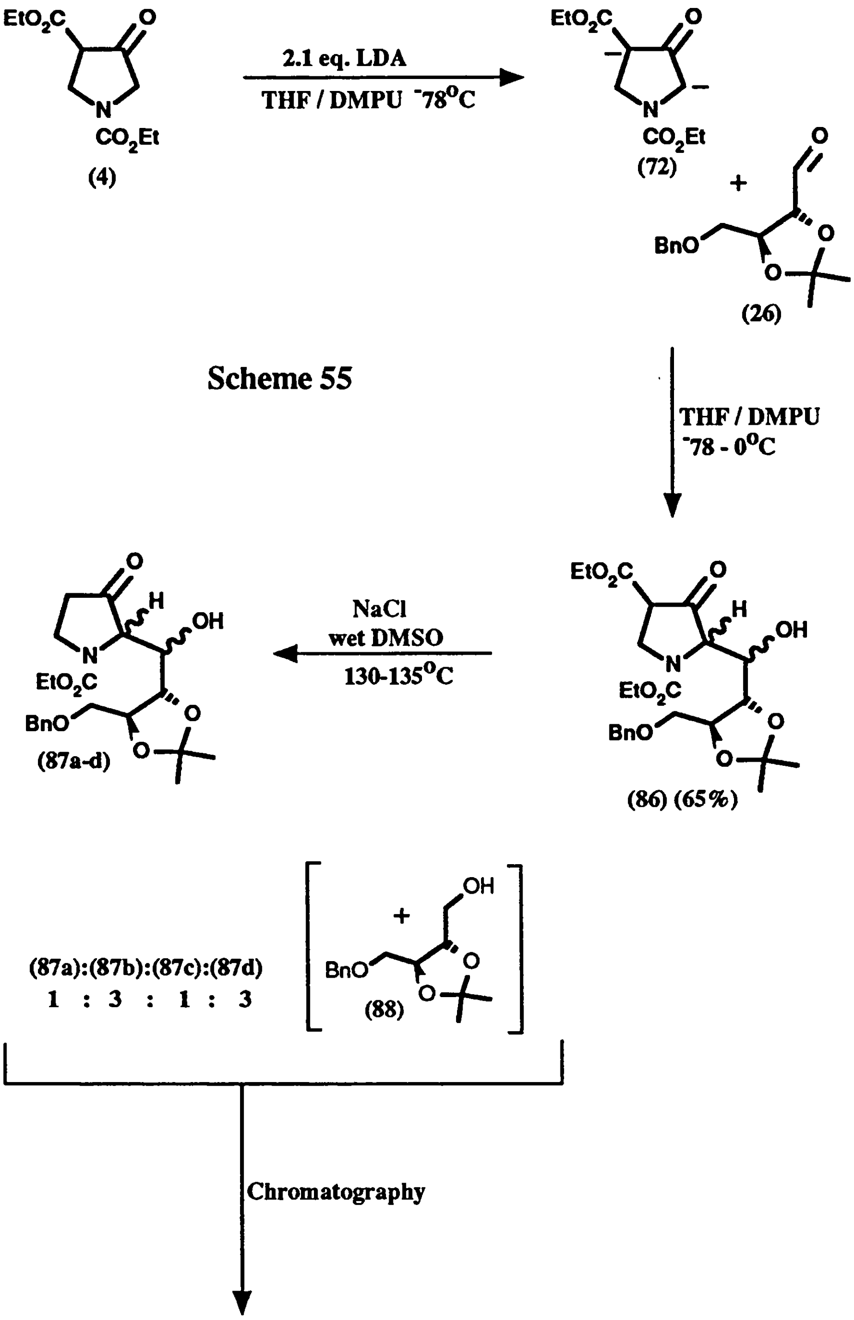
3 *Synthetic Studies Directed Towards Castanospermine*

3.1 *Retrosynthetic Analysis*

A retrosynthetic analysis for the target molecule is outlined in Scheme 53. The aldol-type reaction of dianion **(72)** with chiral aldehyde **(26)**[138,139] emerged as a key step in this plan, and the diastereoselectivity available in such a reaction was a major consideration. Before the synthetic plan was addressed experimentally, a model study involving the synthesis of a pyrrolizidine was undertaken, which yielded some useful information pertaining to some of the later steps in the proposed synthesis.

3.2 *The Synthesis of a Pyrrolizidine*

The 2-substituted-3-pyrrolidinone **(75e)** (see Table 5) was converted to the pyrrolizidine **(83)** by the route shown in Scheme 54. Before the ethoxycarbonyl group could be removed from the heterocyclic nitrogen atom, the ketone function in **(75e)** had first to be protected. Preparation of the cyclic ketal **(81)** from **(75e)** proceeded in 80% yield, and subsequent deprotection of the nitrogen atom was achieved using potassium hydroxide in diethylene glycol[178] to afford the crude amine **(82)**. *O*-Debenzylation of **(82)** was then accomplished by hydrogenolysis, yielding the amino alcohol **(83)** in 77% overall yield from **(81)**. The cyclization[182] of **(83)** was effected using triphenylphosphine and carbon tetrabromide in the presence of Hünig's base to give the pyrrolizidine **(84)**, a protected derivative of 1-ketopyrrolizidine,[184] in a yield of 27% which was not optimized. Pyrrolizidine **(84)** was characterized as the picrate salt according to a general procedure.[183] Execution of the transformations shown in Scheme 54 established a protocol for the double deprotection required for the preparation of an amino alcohol from the



Scheme 55

(87b) (13.2%) [+(88)]

(87d) (11.3%)

[(87a-d) (approx. 21%)]

corresponding *N*-ethoxycarbonyl-*O*-benzyl-protected precursor, as well as a method for the dehydrative cyclization of the amino alcohol. Armed with these results we proceeded with the planned synthesis of our target molecule.

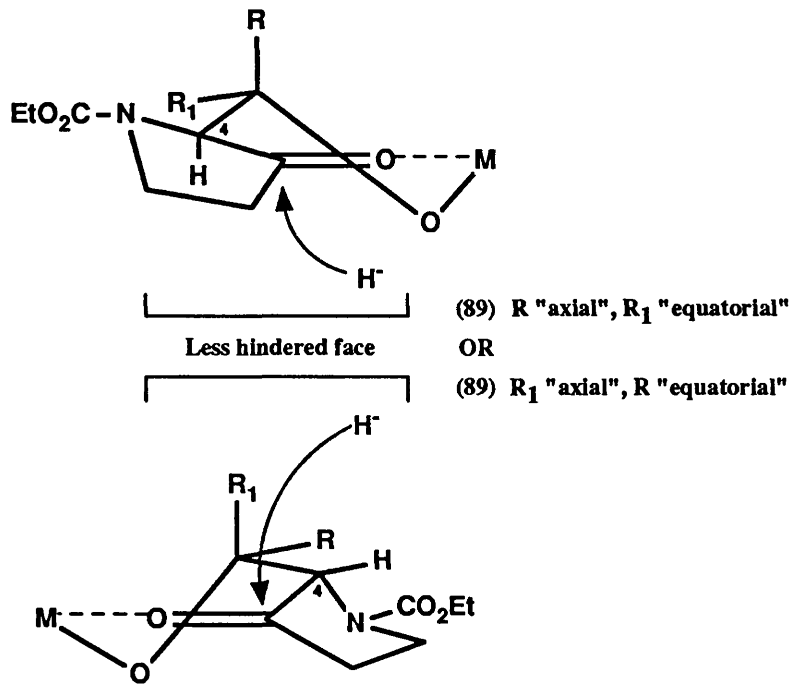
3.3 The Aldol-type Reaction of the Dianion with a Chiral Aldehyde and the Deethoxycarbonylation of the Adduct

The reaction of dianion **(72)** with aldehyde **(26)** provided the adduct **(86)** in 65% yield as a complex mixture (Scheme 55). Deethoxycarbonylation of this mixture afforded the aldol product **(87)** as a mixture of all four diastereoisomers, and analysis of the crude product mixture from subsequent runs by HPLC indicated that the diastereoisomers **(87a)**:**(87b)**:**(87c)**:**(87d)** were present in an approximate ratio of 1:3:1:3. A quantity of alcohol **(88)** was also present in the mixture and the proportion of **(88)** present varied according to the run. When the aldol-type condensation was performed on a large scale (50 mmol), a substantial proportion of **(88)** (approximately 16 mol%) was detected in the deethoxycarbonylation product mixture (see Experimental and Appendix 1, HPLC trace 1). The aldehyde **(26)** may have been contaminated with **(88)** (the precursor to **(26)**) before use in the dianion reaction, although the proportion of alcohol impurity observed was unexpectedly high. The formation of **(88)** from **(26)** during the aldol-type reaction *via* a competing reduction process is also a possibility, however, to the best of our knowledge, the reduction of α-alkoxy aldehydes *via* hydride transfer from LDA is unprecedented, although certain ketones are readily reduced in this way.[94a,185]

The components of the aldol product mixture were separated by semi-preparative HPLC (see Appendix 1) and purified samples of each diastereoisomer were obtained for analysis by ^{1}H nmr spectroscopy and mass spectrometry (see Experimental and Appendix 2). As with many of the simple alkyl and aldol adducts **(75)** (see Table 5), substantial signal-broadening in the ^{1}H nmr spectra of these diastereoisomers was observed due to amide-type resonance, although sharp spectra were obtained at elevated temperatures (see Appendix 2). During the HPLC separation of the aldol product mixture, it was found that, while **(87c)** and **(87d)** were relatively easy to isolate, the separation of the components of the remaining mixture of **(88)**, **(87a)** and **(87b)** was difficult to achieve. A different type of HPLC column was employed for this separation and clean samples of **(88)** and **(87b)** were obtained, however, the remaining fraction did not contain purified **(87a)**, as expected, but consisted of a 70:30 mixture of **(87a)**:**(87c)**. Since the original three-component mixture did not contain **(87c)**, then either **(87a)** or **(87b)** underwent isomerization (presumably *via* epimerization at C-2) to **(87c)** during this separation. A subsequent attempt to separate **(87a)** and **(87c)** from the 70:30 mixture resulted in the isolation of **(87a)** which was still contaminated with **(87c)** (approximately 10 mol%), suggesting that it is the minor diastereoisomer **(87a)** that is susceptible to this mode of isomerization.

Such phenomena serve to remind us that we must be wary of inferring information about the diastereoselectivity of the condensation reaction from the ratio of diastereoisomers **(87)** observed in the crude product mixture, since isomerizations may also be possible during the chromatography of the initial adducts **(86)**, or during the deethoxycarbonylation step.

The mixture of diastereoisomers **(87)** obtained from a medium scale (10 mmol) dianion reaction was subjected to repeated chromatography on silica gel, using petrol-ethyl acetate solvent systems as eluants, in an attempt to separate the major diastereoisomers. Under these conditions, the order of elution of the close-running isomers **(87a)** and **(87b)** was reversed compared to that observed during the HPLC analysis (see Appendix 1, HPLC trace 1), so



M = Metal

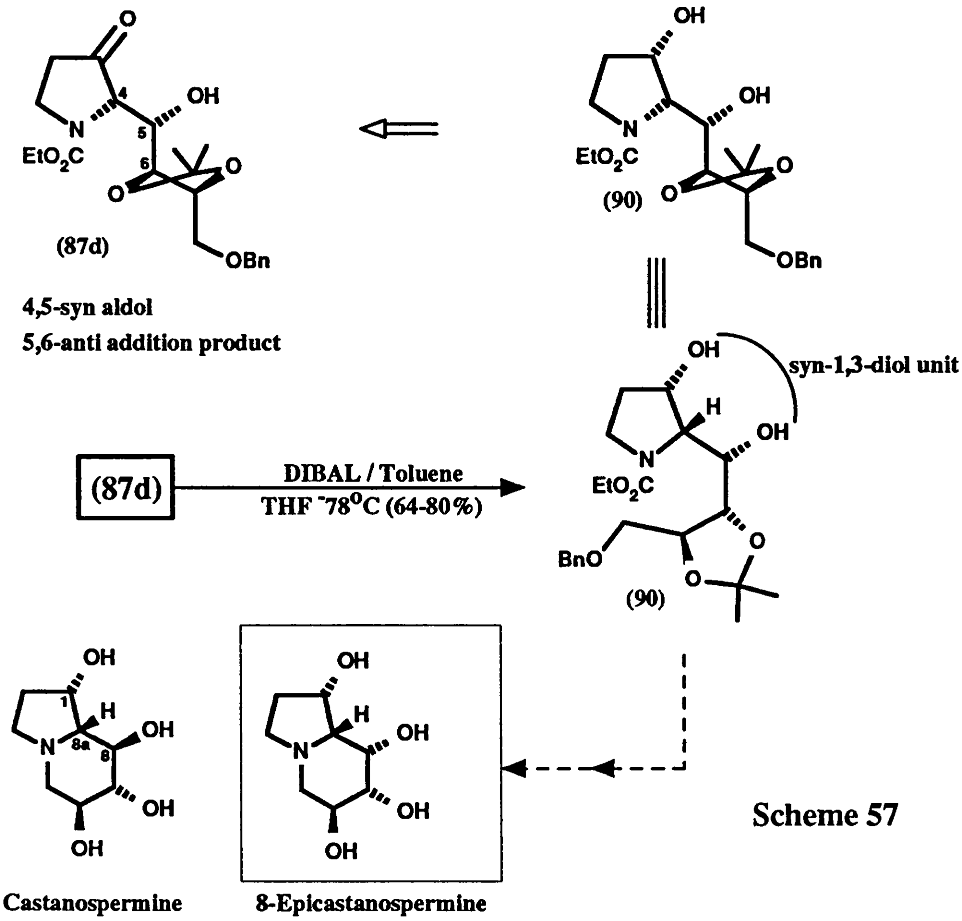
Scheme 56

that major diastereoisomer **(87b)** was eluted from the column first, followed by a mixture of diastereoisomers which included **(87a)** and **(87c)**, and finally the other major isomer **(87d)**. Although the major diastereoisomers were not well resolved, useful quantities of **(87b)** and **(87d)** were obtained by collecting early and late fractions respectively, from each successive column. Analysis of these purified samples by HPLC showed that **(87b)** was contaminated with alcohol **(88)** (20 mol%) as well as a small quantity of **(87a)**, and **(87d)** was contaminated with a trace amount of **(87c)** (see Appendix 1, HPLC traces 2 and 3). The yield of **(87b)** was 14.1% from β-keto ester **(4)**, accounting for contamination by **(88)**, and diastereoisomer **(87d)** was obtained in 11.7% yield from **(4)**. These isomers were adjudged pure enough for subsequent reactions.

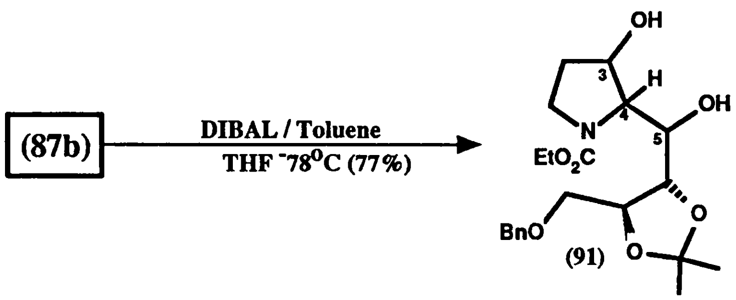
3.4 The Stereoselective Reduction of the Major Aldol Diastereoisomers

In the model study, the ketone group of **(75e)** was protected as a ketal before the secondary amine function was released (see Scheme 54). In the case of synthetic intermediates **(87b)** and **(87d)**, stereoselective reduction of of the ketone group was required in order to install the required hydroxyl group at C-3 of the pyrrolidine nucleus. Since carbons C-1 and C-8a of castanospermine bear hydrogens that are *cis* to one another, a method for the stereoselective reduction of these aldols to the *cis*-2-substituted-3-hydroxypyrrolidines was required. We reasoned that hydride attack of the ketone function of a bicyclic chelate **(89)**, derived from the corresponding β-hydroxy ketone, should occur from the least hindered face; i.e. from the opposite side to the C-4 substituent (Scheme 56). Thus, the reduction would be, in effect, controlled by the configuration at C-4.

This premise was supported by the observed selectivity in the DIBAL reduction of a carbohydrate-based aldol derived from a heterocyclic enolate,[186]



Scheme 57



Single diastereoisomer isolated
? Stereochemistry at C-3, C-4 and C-5 ?

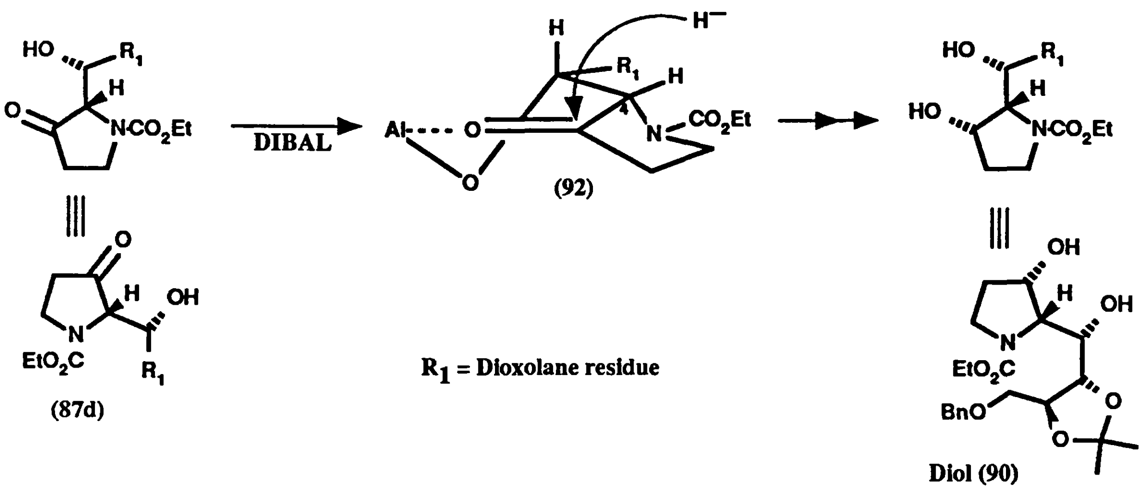
Scheme 58

and a similar model has been invoked by Ghera and Shoua to explain the highly stereoselective addition of Grignard reagents to 2-(1-hydroxyalkyl)-cyclopentanones.[187] Related metal-oxygen chelates have also been implicated in the reduction of acyclic aldols to *syn*-1,3-diols using DIBAL[188], and other reducing systems.[189]

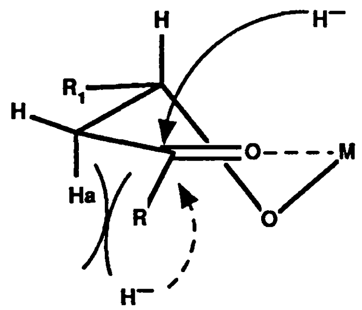
Reduction of aldol **(87d)** using DIBAL afforded diol **(90)**, a potential precursor to 8-epicastanospermine, in up to 80% yield as the only detected isomer (Scheme 57). The stereochemistry of the product was not determined at this point, but an X-ray crystallographic analysis of the amino alcohol derived from **(90)** (see below) confirmed that the reduction had yielded the *syn*-1,3-diol. Thus, assuming that no epimerization at C-4 had occurred during the reduction, the stereochemistry of **(87d)** could be assigned as the *syn*-aldol, *anti*-addition product.

Reduction of the other major aldol diastereoisomer **(87b)** also proceeded in a highly stereoselective manner under essentially identical conditions, to give a diol **(91)** in 77% yield (Scheme 58) Only one diastereoisomer could be detected by ^{1}H and ^{13}C nmr spectroscopy but the stereochemistry of **(91)** could not be assigned at this point.

The stereochemical outcome of the reduction of diol **(90)** can be rationalized by assuming that the reaction proceeds *via* a chelated intermediate **(92)**, derived from aldol **(87d)**, with the dioxolane residue adopting a pseudo-equatorial orientation. (Scheme 59). Hydride attack from the less hindered side of the chelate then leads to the observed product **(90)**. It should be noted that the formation of *syn*-1,3-diols from simple aldols has been explained by invoking a chelate model, where hydride attack of the ketone occurs so as to avoid an unfavourable interaction with the pseudo-axial

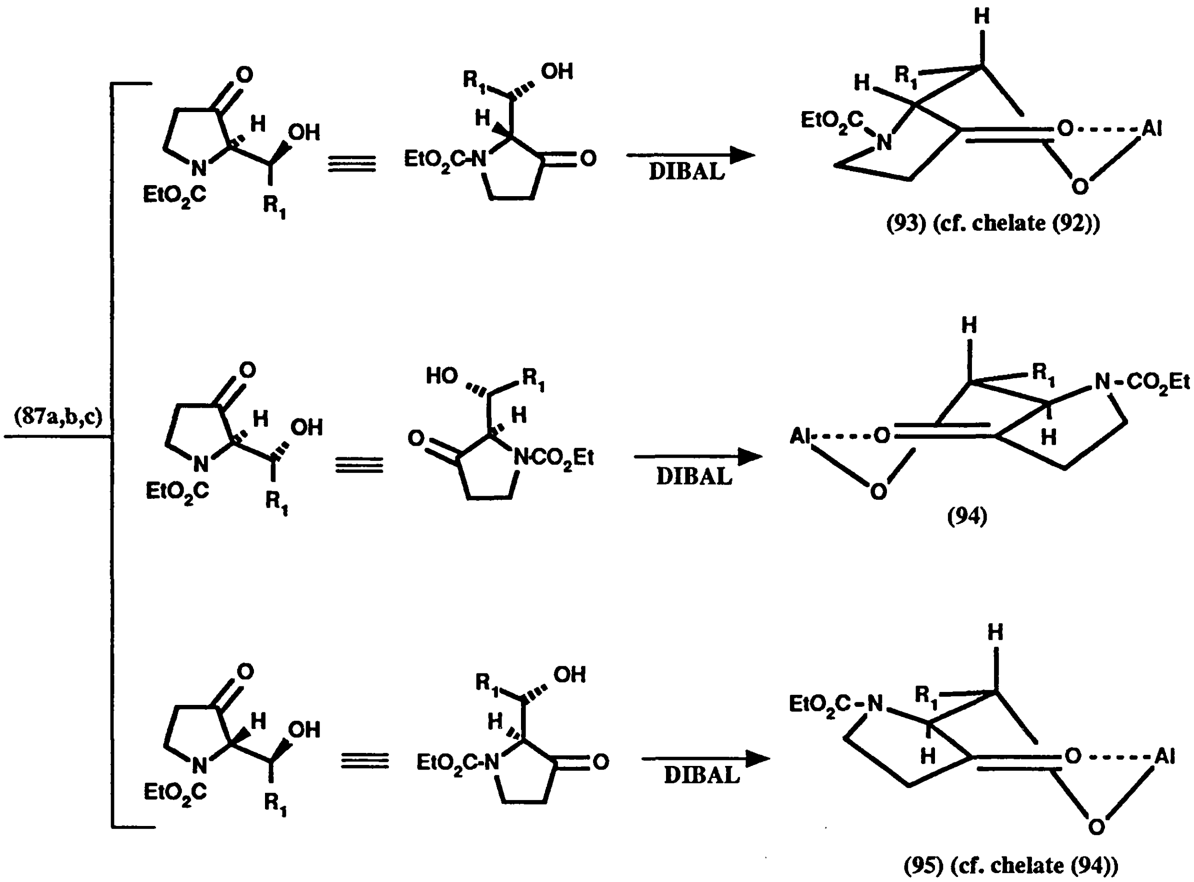


Scheme 59



M = Metal

Fig. 3



Scheme 60

α-proton H_a[188,189b] (Fig. 3). Although the C-4-N bond in **(92)** is not as axially disposed as C-H_a in Fig.3, owing to the cyclic constraint of the pyrrolidine ring, this effect would be expected to reinforce the steric bias imparted by the convex nature of the chelate. Inspection of the proposed chelated intermediates **(93)**, **(94)** and **(95)** for the remaining aldol diastereoisomers indicates that a reinforcement of the two controlling elements should be operative for **(93)**, but with **(94)** and **(95)** the effects are again in opposition (Scheme 60). Similarly, Evans has noted that α-substituents in chelates derived from acyclic aldols may either reinforce or disrupt the *syn*-selective trends observed in the reduction of α-unsubstituted aldols.[190]

With the aldol isomers **(87)**, this simplistic model must be regarded with a degree of caution, since the possibility of a coordinative interaction between the aluminium reagent and either the *N*-ethoxycarbonyl group or the dioxolane residue has been ignored.

3.5 *Stereochemical Aspects of the Aldol-type Reaction*

Very little work has been done on aldol-type condensations involving dianions derived from β-keto esters. Sakai and coworkers showed that dianions generated from certain acyclic β-keto esters underwent reaction with aldehydes to give predominantly the *anti*-aldol-type adducts, and rationalized this observation in terms of non-chelation controlled addition.[176a] In our case, the major diastereoisomer **(87d)** corresponds to the *syn*-aldol-type adduct, assuming that no isomerization had occurred during the deethoxycarbonylation or purification procedures. The face selectivity in addition of dianion **(72)** to the chiral aldehyde **(26)** appeared to be accordance with the preferences normally observed with enolate additions to this aldehyde,[138,192] and to (R)- or (S)-glyceraldehyde,[191] which result in the formation of *anti*-addition products.

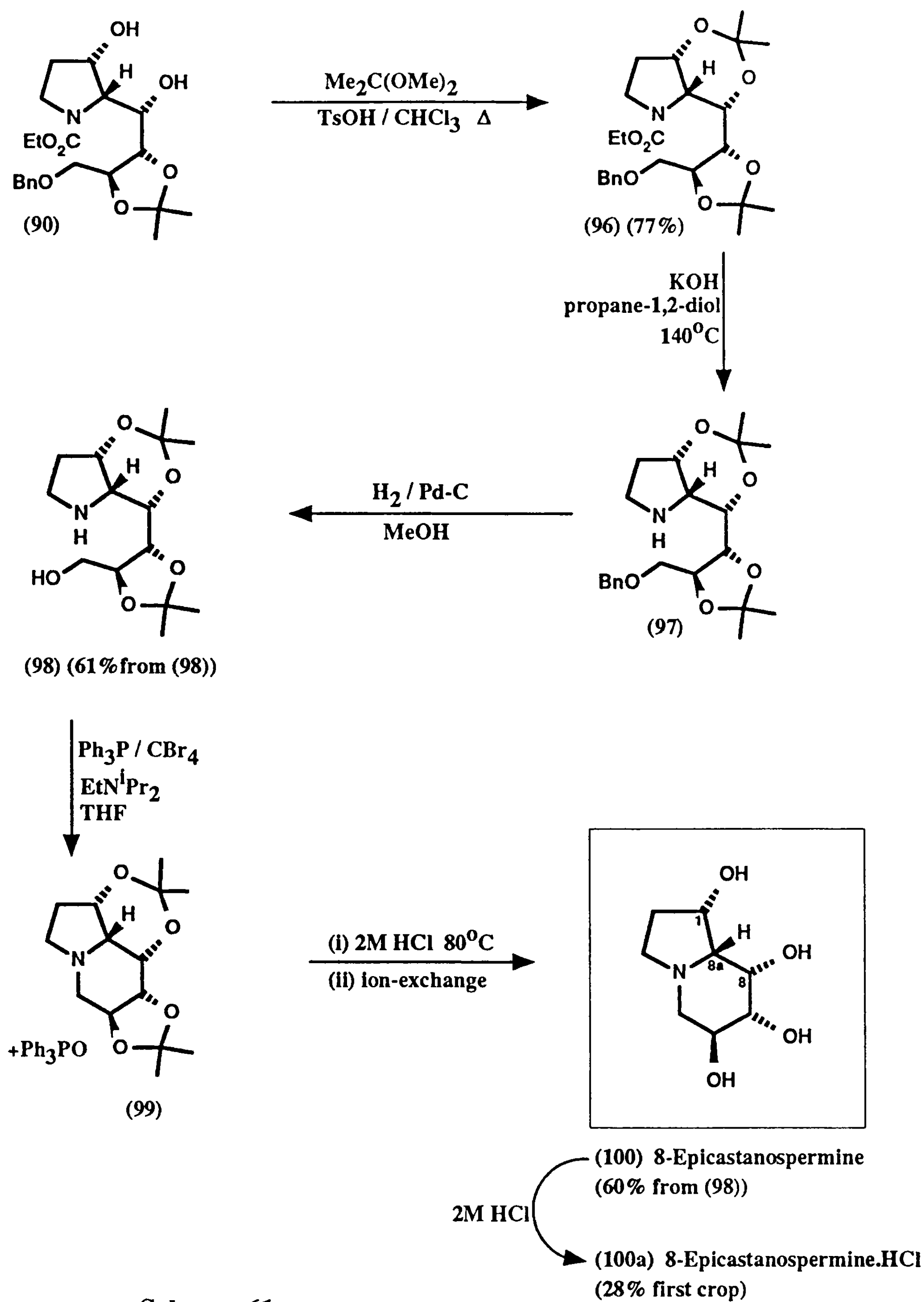
Non-chelation controlled addition of the dianion to the aldehyde would explain the observed selectivity in this aldol-type reaction.

In contrast to the scant attention devoted to such dianion reactions, there is a considerable amount of information available on the diastereoselectivity of aldol reactions involving enolates. While it is known that, in general, lithium Z-enolates lead reliably to *syn*-aldols,(193) the products obtained from lithium E-enolates (which include heterocyclic lithium enolates) are less predictable, although *anti*-aldols often predominate(180,191,193) especially under thermodynamic conditions.(191) Fraser-Reid and his associates have shown that the reaction between a heterocyclic zinc enolate (E-enolate) and (R)-glyceraldehyde leads to formation of the unexpected *syn*-aldol product(186) (with expected *anti*-additon to the aldehyde). These workers proposed that a secondary chelation effect may account for this result, although non-chelation controlled addition to the aldehyde would also explain the observed selectivity.

Various lithium-oxygen chelating interactions may be envisioned in the aldol-type reaction of dianion **(72)** with aldehyde **(26)**. However, it must be stressed that models proposed for the aldol reactions of enolates may not be applicable to the corresponding reactions of β-keto ester dianions.

3.6 The Synthesis of 8-Epicastanospermine and Tetrahydroxyindolizidine (105)

Further batches of the major aldol isomers **(87b)** and **(87d)** were prepared from a large scale (50 mmol) reaction of dianion **(72)** with aldehyde **(26)**, followed by deethoxycarbonylation. In this case, repeated chromatography furnished **(87b)** as a 1:1 mixture with alcohol **(88)** (13.2% of



Scheme 61

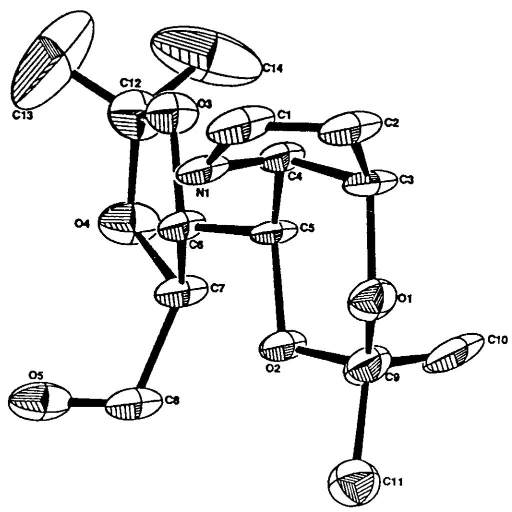
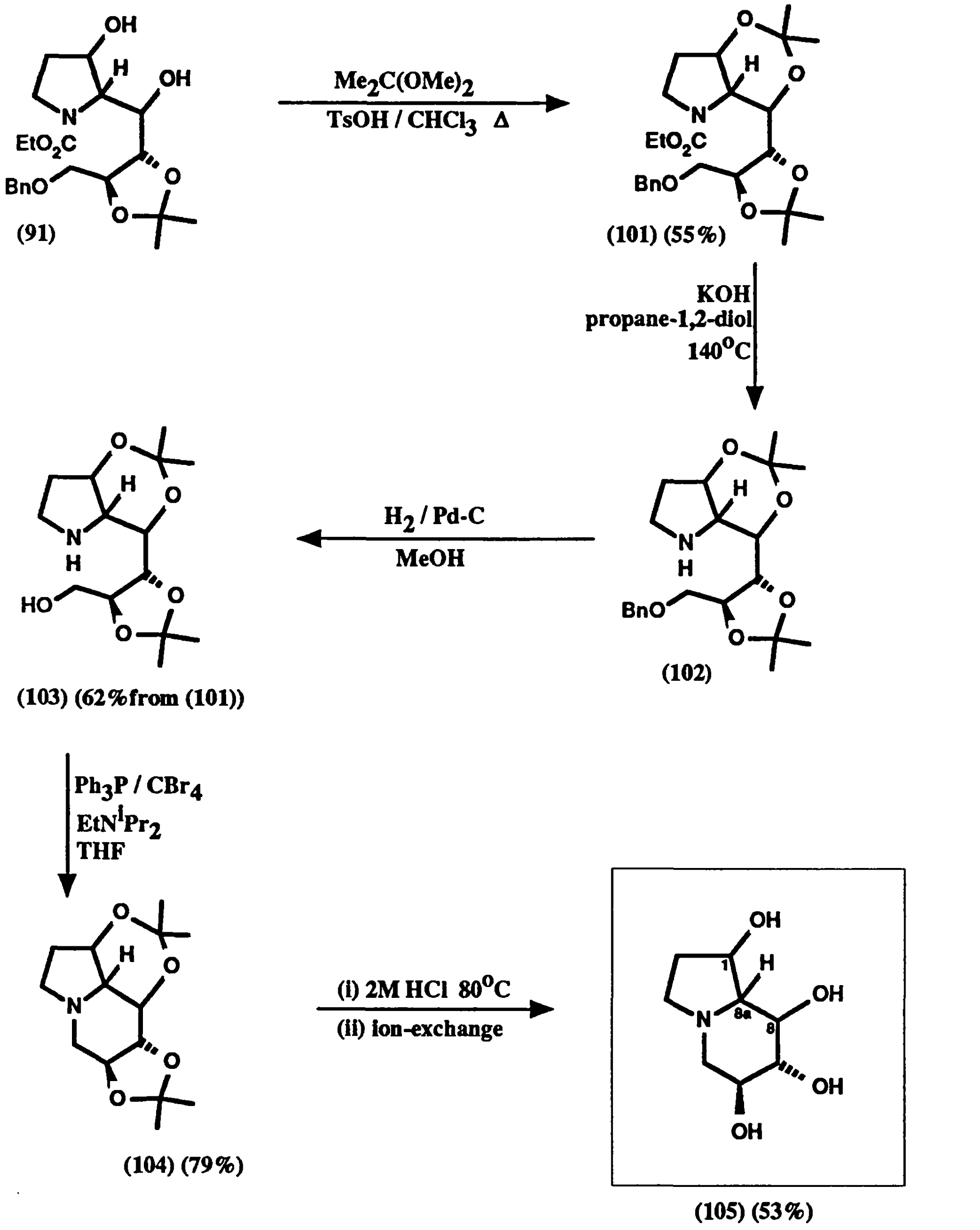


Fig. 4

ORTEP PLOT OF (98)

(87b)). Aldol **(87d)** was obtained in a practically pure state in 11.3% yield. Because of the difficulty encountered upon the attempted separation of **(87b)** from **(88)**, the mixture was subjected to reduction with DIBAL, and the diol **(91)** was isolated cleanly from this reaction, albeit in diminished yield (see Experimental). A multi-gram quantity of aldol **(87d)** was reduced as before to give **(90)**.

Sufficient quantities of each of diols **(90)** and **(91)** were now available for further transformations. The synthesis of 8-epicastanospermine was completed in five steps from diol **(90)**, as shown in Scheme 61. It was considered advantageous to protect the 1,3-diol functionality of **(90)**, in order to facilitate the handling of subsequently derived intermediates. We found that the 1,3-diol acetonide unit served admirably for this purpose. Thus, *bis*-acetonide **(96)** was prepared in 77% yield by acid-catalyzed transketalization.[194] The double deprotection protocol established during the model study (see Scheme 54) was employed for the conversion of **(96)** to the amino alcohol **(98)** *via* amine **(97)** which was not characterized. Diethylene glycol could be replaced by a 4:1 mixture of propane-1,2-diol[195] and methanol as solvent for the *N*-deprotection step. The highly crystalline amino alcohol **(98)** was obtained in 61% yield from **(96)** after recrystallization, and the stereochemistry of the product was determined by single-crystal X-ray analysis (Fig. 4). Assembly of the indolizidine framework was accomplished by cyclization of **(98)** according to the conditions described in the model study,[182] to give tetracycle **(99)**. Very recently, related cyclizations of 1,4- and 1,5-amino alcohols using the Mitsonubu reagent[196] have been reported by Bernotas and Cube for the construction of azacycles and azabicycles, including hydroxylated indolizidine derivatives.[197] The triphenylphosphine oxide produced in the cyclization reaction of **(98)** could not be separated from **(99)** by chromatography, however, this by-product did not interfere with the subsequent hydrolysis step. The final



? Stereochemistry at C-1, C-8 and C-8a ?

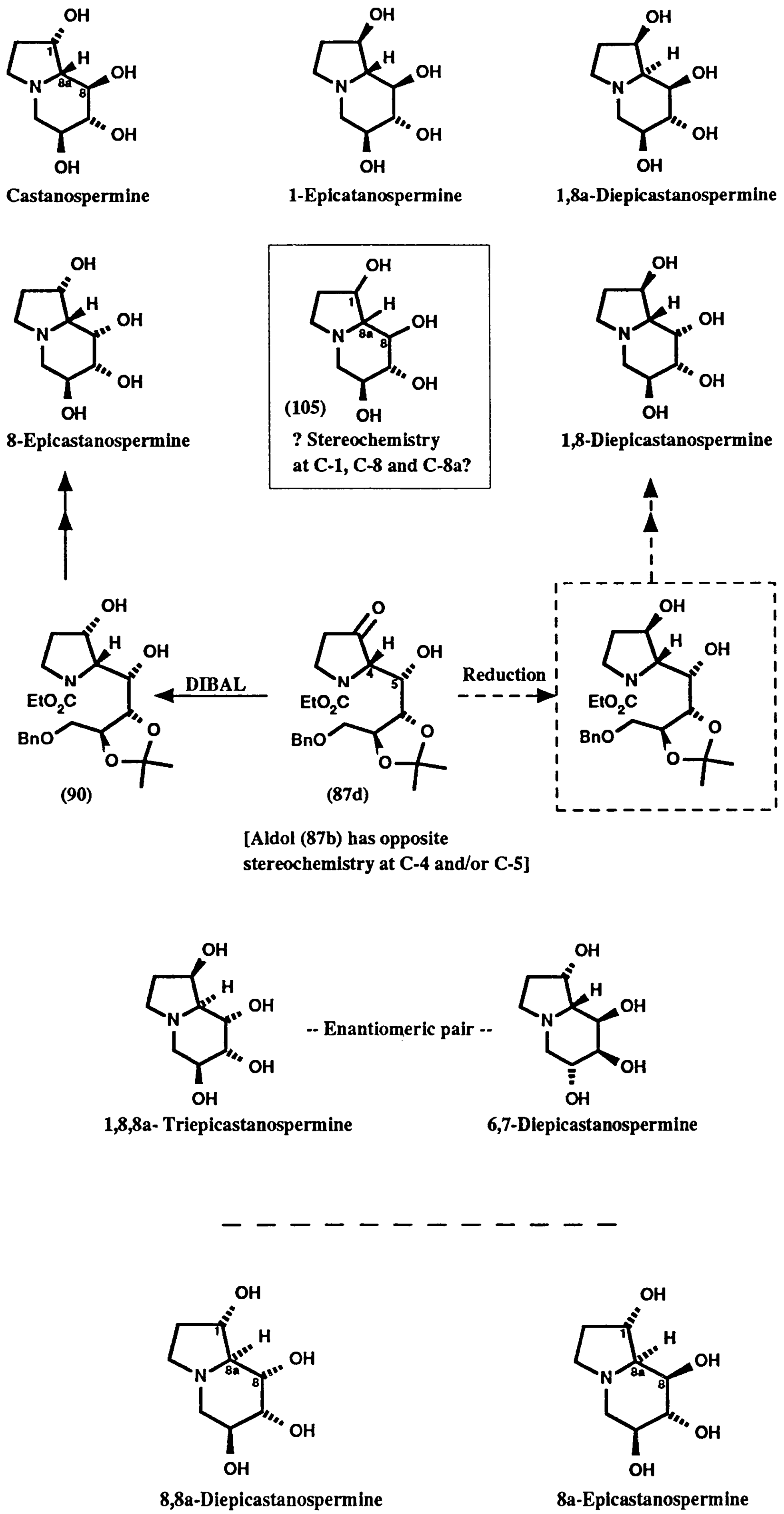
Scheme 62

deprotection of **(99)** was achieved by treatment with 2M aqueous hydrochloric acid[198] to give the crude hydrochloride which was purified by ion-exchange chromatography to afford the free base, 8-epicastanospermine **(100)**, as an oil. The tetrahydroxyindolizidine **(100)** was obtained in 60% yield from amino alcohol **(98)** and in 22% overall yield from aldol **(87d)**, and the ^{1}H nmr and ^{13}C nmr spectra of **(100)** were assigned using ^{1}H-^{1}H and ^{1}H-^{13}C 2D COSY nmr experiments. The synthetic 8-epicastanospermine was fully characterized as the hydrochloride salt **(100a)**, which was obtained as a colourless crystalline solid after recrystallization from methanol ((**100a**): $[\alpha]^{19}_{D}$ +58.4° (c 0.55 in H_2O), m.p. 243-245°C (dec.)). A synthesis of 8-epicastanospermine has been communicated by Ganem *et al*,[63] but a full experimental including spectral data has not been reported to date.

An analogous sequence of reactions was used to convert the diol **(91)** to the tetrahydroxyindolizidine **(105)** (Scheme 62), which was isolated as the free base in 11% overall yield from aldol **(87b)**, and obtained as a colourless crystalline solid after recrystallization from ethanol ((**105**): $[\alpha]^{22}_{D}$ -30.3° (c 0.15 in H_2O), m.p. 168.5-169°C). In this case, the synthetic intermediates **(101)**-**(104)** were all non-crystalline.

3.7 The Possible Stereochemistry of Indolizidine (105)

Although the final product **(105)** was a crystalline solid, all attempts to prepare crystals suitable for X-ray analysis, by recrystallization of the free base or the corresponding hydrochloride, proved unsuccessful. Therefore we resorted to nmr techniques in a bid to elucidate the stereochemistry in this series. In contrast to indolizidine **(99)**, the stereoisomer **(104)** was found to be readily separable from triphenylphosphine oxide by chromatography, and was available in a pure state. This molecule appeared to be ideally suited to

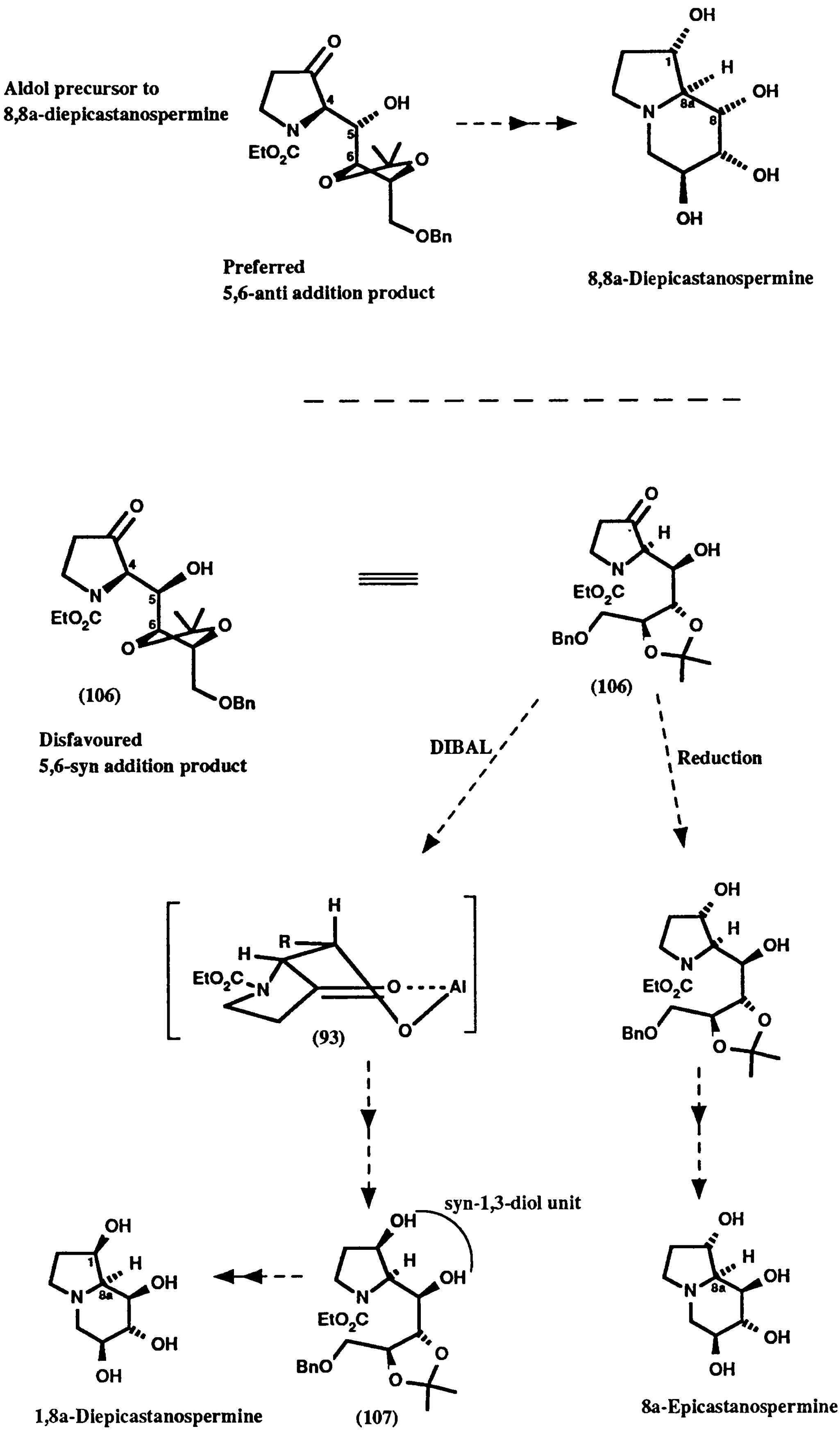

Castanospermine
1-Epicatanospermine
1,8a-Diepicastanospermine
8-Epicastanospermine
(105)
? Stereochemistry
at C-1, C-8 and C-8a?
1,8-Diepicastanospermine
DIBAL
Reduction
(90)
(87d)
[Aldol (87b) has opposite
stereochemistry at C-4 and/or C-5]
1,8,8a- Triepicastanospermine
-- Enantiomeric pair --
6,7-Diepicastanospermine
8,8a-Diepicastanospermine
8a-Epicastanospermine

Scheme 63

structural analysis by n.O.e. experiments since all eleven indolizidine ring protons were well defined in the ^1H nmr spectrum, and were assigned using a ^1H-^1H 2D COSY experiment. However, the n.O.e. difference experiments were hampered by the apparent instability of **(104)**, which led to the formation of an impurity, possibility as a result of acetonide cleavage in deuteriochloroform, and the results of these experiments were inconclusive; experiments run in benzene-d_6 proved equally unsuccessful. Consequently, the absolute stereochemistry at C-1, C-8 and C-8a of **(105)** could not be determined in this way.

However, a number of possibilities may be immediately excluded (Scheme 63). Of the eight possible diastereomeric structures for **(105)**, the known compounds(62,63,66,74) castanospermine, 1-epicastanospermine, 1,8a-diepicastanospermine and, of course, 8-epicastanospermine are precluded, on the basis of spectral data. 1,8-diepicastanospermine is also untenable as a possible candidate, since the only aldol isomer with the correct stereochemistry at C-4 and C-5 for elaboration to this product was **(87d)** (which underwent reduction with DIBAL to give **(90)**, a precursor to 8-epicastanospermine) and therefore, aldol **(87b)** (which was reduced under the same conditions as **(87d)**), could not provide the 1,8-diepi-isomer. 1,8,8a-Triepicastanospermine may also be excluded since the enantiomer, 6,7-diepicastanospermine, has been prepared by Sih *et al*(73) and the spectral data for this compound is clearly different from that of **(105)**.(199) This leaves 8a-epicastanospermine and 8,8a-diepicastanospermine as the only remaining possibilities. The synthesis of these stereoisomers and their isolation from natural sources have not been reported.

Because indolizidine **(105)** was prepared from a major diastereoisomer **(87b)**, the more reasonable structure for **(105)** is


Aldol precursor to
8,8a-diepicastanospermine
Preferred
5,6-anti addition product
8,8a-Diepicastanospermine
(106)
Disfavoured
5,6-syn addition product
(106)
DIBAL
Reduction
(93)
syn-1,3-diol unit
1,8a-Diepicastanospermine
(107)
8a-Epicastanospermine

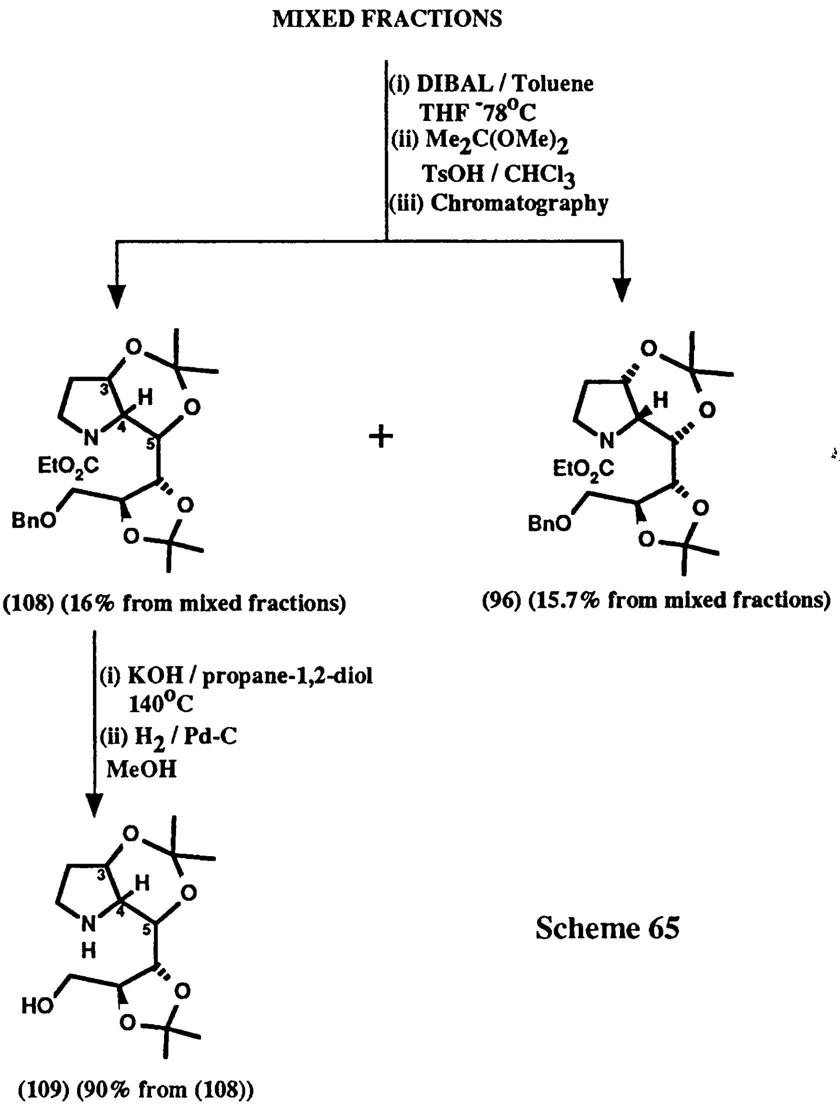
Scheme 64

8,8a-diepicastanospermine, since the proposed aldol precursor would result from favoured *anti*-addition of dianion **(72)** to aldehyde **(26)**, so that **(87b)** differs from **(87d)** merely in the stereochemistry at C-4 (i.e. **(87b)** is the *anti*-aldol product). For the alternative, 8a-epicastanospermine, disfavoured *syn*-addition of **(72)** to **(26)** would be required, in order to produce the aldol precursor **(106)** (Scheme 64). Furthermore, the chelation controlled reduction of **(106)** would be expected to afford the *syn*-1,3-diol **(107)** *via* chelate **(93)** (see Scheme 59) and **(107)** is a precursor of the known tetrahydroxyindolizidine 1,8a-diepicastanospermine[(74)], which is clearly different from **(105)**. The foregoing arguments support a tentative assignment of **(105)** as 8,8a-diepicastanospermine, however, additional information is required before the stereochemistry of this isomer can be unequivocally defined.

3.8 Reactions Performed on the Mixed Aldol Fractions

Finally, some of the reactions discussed above were applied to the mixture of diastereomeric aldols present in the mixed fractions obtained from the chromatography of **(87a-d)** (50 mmol preparation). A portion of this mixture was reduced with DIBAL to give a mixture of diols, homogeneous by TLC, which were immediately converted to a corresponding mixture of *bis*-acetonides. This mixture contained a number of products which were well resolved by TLC. The two major components were easily separable by chromatography on silica gel, and the first-eluted major product was characterized as a *bis*-acetonide **(108)**, and was clearly different from **(96)** and **(101)** (Scheme 65). This new *bis*-acetonide isomer was obtained in 16% yield from the original aldol mixture. The other major product, isolated in 15.7% from the aldol mixture was found to be identical to **(96)**.

Double-deprotection of **(108)** proceeded smoothly to give the new



Scheme 65

(Stereochemistry at C-3,C-4 and C-5 of (108) and (109) unknown) amino alcohol **(109)** as an oil in 90% yield. Interestingly, the attempted cyclization of this material using the conditions employed previously failed to give any of the desired indolizidine, and a low yield of the starting material **(109)** was recovered instead. The absolute stereochemistry of **(108)** and **(109)** was not determined.

3.9 Summary

The synthesis two stereoisomers of castanospermine has been achieved in eight steps from readily available starting materials, using a novel aldol-type reaction of a β-keto ester dianion with a chiral aldehyde as the key step. The synthesis of 8-epicastanospermine was accomplished in six steps from aldol precursor **(87d)** in an overall yield of 22%, whereas the parallel synthesis of the novel tetrahydroxyindolizidine **(105)** proceeded in an overall yield of 11% from aldol **(87b)**. Control of the diastereoselectivity of the aldol-type reaction would constitute an attractive extension to this synthetic strategy and work in that direction is in progress.

EXPERIMENTAL

EXPERIMENTAL

Instrumentation and Experimental Techniques

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and peaks are reported (υ_{max}) in wavenumbers (cm^{-1}). The abbreviation "br" is appended to a peak to indicate significant broadening. Spectra of liquid samples were taken as thin films on sodium chloride plates. Spectra of solid samples were taken as nujol mulls.

Routine mass spectra were obtained in the electron impact mode (E.I.) with an ionizing potential of 70eV and in the chemical ionization mode (C.I.), with isobutane as reagent gas. Mass spectra were also obtained in the electron impact mode with low ionizing potential (Low eV E.I.) where appropiate (variable ionizing potential in the range 5-30 eV). These along with high resolution accurate mass determinations in the (E.I.) mode were recorded with a VG Analytical 7070E instrument and a VG2000 data system. High resolution accurate mass determinations in the (C.I.) mode were recorded using the S.E.R.C facility at the University of Swansea. Where possible, the molecular ion peak is indicated along with all sizeable fragments.

Proton magnetic resonance (^{1}H nmr) spectra were recorded at 270MHz, unless otherwise stated, on a Jeol GNM GX FT 270 spectrometer. ^{1}H nmr spectra were also recorded at 60MHz on Hitachi Perkin-Elmer high resolution R-23B and Varian Anaspect EM-360 spectrometers, at 250MHz and at 400MHz on Bruker spectrometers (Smithkline Beecham Research, Harlow), and at 400MHz on a Jeol GNM GX FT 400 spectrometer. Carbon 13 magnetic resonance (^{13}C nmr) spectra were recorded on a Jeol GNM GX FT 270 spectrometer operating at 68MHz and using 90 and 135 DEPT pulse sequences to aid in multiplicity determination.

Proton and ^{13}C nmr spectra were recorded, unless otherwise stated, in $CDCl_3$, and are expressed in parts per million (δ) downfield from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), heptet (hept.) and multiplet (m). The abbreviation "br" is appended to a multiplicity to indicate significant broadening.

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser. Optical rotations were measured using a Perkin-Elmer 141 polarimeter with concentration (c) expressed in g/100ml.

Thin layer chromatography (TLC) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light (when possible) or using a reagent (typically a 7% (w/v) solution of dodeca-molybdophosphoric acid in methanol) that would give a colour change with the functional groups present, as described in "Dyeing Reagents for Thin Layer and Paper Chromatography", E. Merck, Darmstadt, 1980.

Unless otherwise stated petrol refers to that fraction of petroleum spirit boiling in the range 60-80°C. Organic solvents used as eluants in chromatography were dried and distilled prior to use except for chloroform, which was used without distillation.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 (Merck 9385) (flash) and 60H silica gel (Merck 7736) for reaction component seperations. A pressure gradient was developed using small, commercially available hand bellows (Gallenkamp). In all cases columns were prepared in the least polar solvent of the eluant mixture and chromatography was carried out with the least polar solvent as initial eluant, then eluting with solvent mixtures of steadily increasing polarity. Material to be chromatographed was preadsorbed onto the column support and applied as a thin layer to the top of the column. Preparative thin layer chromatography was performed using Merck 60 F_{254} silica gel, glass supported plates.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was redistilled immediately prior to use.

Glassware used for water sensitive reactions was baked in an oven at 120°C for approximately 12h and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirrer bars were, however, additionally flame dried under a stream of dry nitrogen. In all experiments the excess solvent was removed with a Büchi rotary evaporator using a water aspirator at room temperature (unless otherwise stated) to avoid unnecessary decomposition. All yields quoted are of purified products and are uncorrected unless otherwise stated.

All other reagents and solvents were purified and dried, when required, according to accepted procedures.[201]

Diethyl 4-Oxo-1,3-pyrrolidinedicarboxylate (4)

A slight modification of the procedure described by Rapoport[122] was employed: A 3-litre, three-necked, round bottomed flask equipped with an overhead mechanical stirrer and a reflux condenser was charged with absolute ethanol (1500 ml). The flask was immersed in an ice-bath and sodium metal (15.2 g, 0.66 mol) was added in small lumps with vigorous stirring. After 1h the ice-bath was removed and stirring was continued until all the sodium had dissolved. To the resulting solution was added, with stirring, ethyl *N*-ethoxycarbonyl glycinate[121] (115 g, 0.66 mol) followed by a solution of ethyl acrylate (56.8 g, 59.4 ml, 0.66 mol) in absolute ethanol (50 ml). The stirred mixture was then heated under reflux for 2h. The resulting deep yellow solution was allowed to cool and most of the ethanol was removed under reduced pressure (rotary evaporator). The viscous golden residue was then poured onto water (1000 ml) and the colourless solid which separated was redissolved by vigorous shaking. The resulting turbid solution was washed with ethyl acetate (2 x 100 ml) and these organic extracts were discarded. The aqueous solution was acidified with 2M aqueous hydrochloric acid (400 ml) and extracted with chloroform (4 x 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **(4)** (81 g, 54%) as a straw-coloured oil which crystallized on standing at room temperature overnight.

This material was pure enough for use in the preparation of ketone **(5)**[114] directly. However, for use in later experiments (see dianion chemistry), the β-keto ester **(4)** (81g) was recrystallized from aqueous ethanol (400-600 ml, 0°C overnight) giving colourless needles which were collected by filtration and freeze-dried overnight. Subsequent crops were obtained by concentration of the mother liquors and similar recrystallization to give a total of up to 30 g (20%) of β-keto ester **(4)** as colourless needles, m.p. 61-62°C (lit. m.p. 62°C[114]).

N-(1,1-Dimethylethyl)-1,4-dioxa-7-azaspiro[4.4]nonane-7-methanimine (2)

To a stirred solution of amine (1)[114] (1.00 g, 7.75 mmol) in toluene (1.5 ml) was added *N,N*-dimethyl-*N'*-*tert*-butyl formamidine[115a] (1.30 g, 10.15 mmol) and ammonium sulphate (20 mg) and the mixture was heated at reflux for 3h. The reaction mixture was then cooled, the solvent was evaporated under reduced pressure and the residue chromatographed on silica gel using ethyl acetate-triethylamine (95:5 v/v) as eluant to give (2) (1.36 g, 83%) as a colourless oil (Found : M^+, 212.1515. $C_{11}H_{20}N_2O_2$ requires 212.1523); υ_{max} (film) 1630 cm^{-1}; δ_H 1.17 (9H, s, CMe_3), 2.07 (2H, t, J 7Hz, 9-H_2), 3.42 (2H, s, 6-H_2), 3.47 (2H, t, J 7Hz, 8-H_2), 3.97 (4H, m, 2-H_2 and 3-H_2), 7.45 (1H, s, CH=N); δ_C 31.0 ($C\underline{Me_3}$), 34.3 (C-9), 45.1 (CH_2), 53.0 ($\underline{C}Me_3$), 54.2 (CH_2), 64.5 (C-2 and C-3), 113.7 (C-5), 147.6 (CH=N); m/z (70eV E.I.) 212 (M^+, 33%), 197 (100), 128 (23), 113 (53), 99 (53), 57 (52).

Ethyl 3,3-Dimethoxy-1-pyrrolidinecarboxylate (7)

A solution of ketone (5)[114] (1.01 g, 6.43 mmol) and toluene-p-sulphonic acid (50 mg) in methanol (50 ml) was heated at reflux for 1h. The mixture was cooled and the solvent removed by evaporation under reduced pressure. The residue was dissolved in ether (50 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (2 x 20 ml). The ether layer was dried ($MgSO_4$) and evaporated under reduced pressure to give (7) (1.10 g, 85%) as a colourless oil which was used without further purification; υ_{max} (film) 1675 cm^{-1}; δ_H 1.26 (3H, t, J 7Hz, $C\underline{H_3}CH_2$), 2.04 (2H, m, 4-H_2), 3.26 (6H, s, OCH_3 x 2), 3.42-3.52 (4H, m, 2-H_2 and 5-H_2), 4.12 (2H, q, J 7Hz, $CH_3C\underline{H_2}$); m/z (70eV E.I.) 203 (M^+, 44%), 188 (25), 174 (50), 172 (30), 115 (23), 101 (85).

3,3-Dimethoxypyrrolidine (8)

To a stirred suspension of (7) (3.11 g, 15.32 mmol) in water (80 ml) was added $Ba(OH)_2.8H_2O$ (7.50 g, 23.77 mmol). The mixture was heated at reflux with efficient stirring for 6h. After cooling, the reaction mixture was filtered and extracted with chloroform (7 x 30 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude amine as a brown oil. Purification by bulb-to-bulb distillation afforded (8) (1.30 g, 66%) as a colourless liquid (b.p. 120-140°C/12mmHg); υ_{max} 3300 (br); δ_H 1.91 (2H, t, J 7Hz, 4-H_2), 2.90 (2H, s, 2-H_2), 3.03 (2H, t, J 7Hz, 5-H_2), 3.24 (6H, s, OCH_3 x 2) (NH not observed); m/z (70eV E.I.) 183 (24%), 144 (24), 100 (38), 89 (100). (Low eV E.I.) 183 (100%).

The amine was further characterized as the hydrogen oxalate salt according to the method of Bühler and Viscontini[114]. An analytical sample was recrystallized from ethanol-ether to give colourless needles, m.p. 105-106.5°C (Found : C, 43.40; H, 7.02; N, 6.34%. $C_8H_{15}NO_6$ requires C, 43.44; H, 6.83; N, 6.33%).

3,3-Dimethoxy-*N*-(1,1-dimethylethyl)-1-pyrrolidinemethanimine (9)

To a stirred solution of amine (8) (3.90 g, 29.73 mmol) in toluene (25 ml) was added *N,N*-dimethyl-*N'*-*tert*-butyl formamidine (4.22 g, 32.91 mmol) and ammonium sulphate (50 mg). The mixture was heated at reflux for 6h. After cooling, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using ethyl acetate-triethylamine (98:2 v/v) as eluant to give (9) (5.74 g, 89%) as a colourless liquid (Found: M^+, 214.1672. $C_{11}H_{22}N_2O_2$ requires 214.1680); υ_{max} (film) 1630 cm^{-1}; δ_H 1.14 (9H, s, CMe_3), 2.03 (2H, t, J 7Hz, 4-H_2), 3.24 (6H, s, OCH_3 x 2), 3.40 (2H, t, J 7Hz, 5-H_2), 3.43 (2H, s, 2-H_2), 7.42 (1H, s, CH=N); δ_C 31.3 ($C\underline{Me}_3$), 32.3 (C-4), 45.0 (CH_2), 49.7 (OCH_3 x 2), 52.9 (CH_2 and $\underline{C}Me_3$), 107.8 (C-3), 147.8 (CH=N); m/z (70eV E.I.) 214 (M^+, 38%), 199 (100), 184 (43), 169 (23), 149 (42), 142 (38), 127

(43), 113 (57), 101 (98), 57 (65).

3,3-Dimethoxy-*N*-(2-phenylethyl)-1-pyrrolidinemethanimine **(10)**

To a stirred solution of amine **(8)** (140 mg, 1.07 mmol) in toluene (1 ml) was added *N,N*-dimethyl-*N'*-(2-phenylethyl)formamidine (230 mg, 1.30 mmol) and ammonium sulphate (5 mg) and the mixture was stirred at reflux for 3h. After cooling, the solvent was evaporated under reduced pressure and the residue chromatographed on silica gel using ethyl acetate-triethylamine (98:2) as eluant to give **(10)** (299 mg, 88%) as a colourless oil; υ_{max} (film) 1630 cm^{-1}; δ_H 2.04 (2H, t, J 7 Hz, 4-H_2), 2.81 (2H, t, J 7.5 Hz, PhC$\underline{H_2}$), 3.26 (6H, s, OCH_3 x 2), 3.39 (2H, t, J 7 Hz, 5-H_2), 3.42 (2H, s, 2-H_2), 3.46 (2H, t, J 7.5 Hz, PhCH_2C$\underline{H_2}$), 7.12-7.31 (6H, m, Ph and CH=N); δ_C 32.5 (CH_2), 39.5 (CH_2), 45.1 (CH_2), 49.8 (OCH_3 x 2), 52.9 (CH_2), 58.2 (CH_2), 107.7 (C-3), 125.8 (Ph_{CH}), 128.1 (Ph_{CH}), 129.0 (Ph_{CH}), 140.6 ($Ph_{Cquaternary}$), 152.3 (CH=N); m/z (Low eV E.I.) 262 (M^+, 7%), 171 (100), 85 (32). Compound **(10)** was not characterized by elemental analysis or high resolution mass determination.

Deketalization of **(10)**

To a solution of **(10)** (242 mg, 0.918 mmol) in acetonitrile (2 ml) was added sodium iodide (0.50 g, 3.33 mmol) followed by trimethylsilyl chloride (217 mg, 0.25 ml, 2.00 mmol) and the mixture was stirred at reflux for 1.5h. After cooling, the mixture was poured onto saturated aqueous sodium hydrogen carbonate solution (10 ml) and extracted with dichloromethane (3 x 5 ml). The combined extracts were dried and evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate-triethylamine (95:5 v/v) as eluant to give **(11)** (50 mg, 25%) as a yellow oil; υ_{max} (film) 1745, 1625 cm^{-1}; δ_H (C_6D_6), 2.30 (2H, m, 4-H_2), 2.99 (2H, t, J 7.5 Hz, PhC$\underline{H_2}$), 3.11 (2H, s, 2-H_2), 3.36-3.53 (2H, m, 5-H_2), 3.62 (2H, t, J 7.5 Hz, PhCH_2C$\underline{H_2}$), 6.98 (1H, s, CH=N), 7.00-7.25 (5H, m, Ph). Compound **(11)** rapidly deteriorated on standing at room temperature.

N,N-Dimethyl-1,4-dioxa-7-azaspiro[4.4]nonane-7-carboxamide **(12)**

To a stirred solution of sodium carbonate (1.30 g, 12.26 mmol) in water (15 ml) was added amine **(1)** (1.29 g, 9.99 mmol) dropwise. The resulting suspension was cooled to 0°C and *N,N*-dimethylcarbamoyl chloride (1.20 g, 1.03 ml, 11.16 mmol) was added dropwise. The reaction mixture was stirred for 30 min at room temperature and then extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed on silica gel using ethyl acetate-triethylamine (98:2 v/v) as eluant to give **(12)** (960 mg, 48%) as a colourless oil. (Found : M^+, 200.1129. $C_9H_{16}NO_3$ requires 200.1164); υ_{max} (film) 1610 cm^{-1}; δ_H 2.00 (2H, t, J 7 Hz, 9-H_2), 2.83 (6H, s, NMe_2), 3.42 (2H, s, 6-H_2), 3.50 (2H, t, J 7 Hz, 8-H_2), 3.97 (4H, s, 2-H_2 and 3-H_2); δ_C 34.3 (CH_2), 38.1 (NMe_2), 46.6 (CH_2), 55.4 (CH_2), 64.7 (CH_2), 113.7 (C-5), 163.2 (C=O); m/z (70 eV E.I.) 200 (M^+, 18%), 99 (31), 72 (100). (Low eV E.I.) 200 (M^+, 100%), 153 (18), 128 (46), 100 (30), 99 (20).

N,N-Dimethyl-3-oxo-1-pyrrolidinecarboxamide **(13)**

To a solution of urea **(12)** (950 mg, 4.74 mmol) in THF (30 ml) was added 2M aqueous hydrochloric acid (30 ml) and the mixture was stirred at room temperature for 72h. The mixture was then extracted with dichloromethane (5 x 20 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using ethyl acetate (100%) as eluant afforded the ketone **(13)** (712 mg, 96%) as a colourless oil (Found : M^+, 156.0884. $C_7H_{12}N_2O_2$ requires 156.0897); υ_{max} (film) 1750 and 1615 cm^{-1}; δ_H 2.54 (2H, t, J 7.5 Hz, 4-H_2), 2.90 (6H, s, NMe_2), 3.78 (2H, s, 2-H_2), 3.81 (2H, t, J 7.5 Hz, 5-H_2); m/z (70 eV E.I.), 156 (M^+, 23%), 128 (10), 113 (7), 72 (100). (Low eV E.I.), 156 (M^+, 100%), 128 (35), 113 (20).

2,3-Dihydro-1-[[*N*-(1,1-dimethylethyl)amino]methylene]-4-(2-hydroxyethoxy)-5-methyl-1*H*-pyrrolium iodide (**17**)

To a stirred solution of (**2**) (213 mg, 1.00 mmol) in THF (5 ml) at -78°C was added *tert*-butyllithium (1.4M in pentane, 1.57 ml, 2.20 mmol) dropwise. The resulting yellow solution was allowed to warm gradually to 0°C over 2h, stirred for 30 min at 0°C then recooled to -78°C. Iodomethane (185 mg, 81 µl, 1.30 mmol) was added and the reaction mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (2 ml) was added, the mixture was stirred vigorously for 5 min and then diluted with water (10 ml) and extracted with dichloromethane (5 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give only a small amount of material. Therefore, the aqueous phase was evaporated under reduced pressure and the residue combined with that obtained from the organic extracts. The combined residues were triturated with dichloromethane (40 ml) and the resulting suspension was filtered to remove solid material. The filtrate was evaporated under reduced pressure and the residue was chromatographed on silica gel using chloroform-methanol (10:1 v/v) as eluant to give a yellow solid which was recrystallized from chloroform-ethyl acetate to give (**17**) (143 mg, 40%) as colourless needles, m.p. 175.5-177°C (Found : C, 41.00; H, 6.79; N, 8.04%. $C_{12}H_{23}IN_2O_2$ requires C, 40.69; H, 6.54; N, 7.91%); υ_{max} (nujol mull) 3380 (br), 1675 cm^{-1}; δ_H 1.56 (9H, s, CMe_3), 1.97 (3H, t, J 2 Hz, 5-CH_3), 2.77 (1H, s(br), OH), 3.00 (2H, m, 3-H_2), 3.84 (2H, t, J 4.5 Hz), 4.06 (2H, t, J 4.5 Hz), 4.39 (2H, t, J 7.5 Hz, 2-H_2), 7.33 (1H, d, J 14 Hz, NC<u>H</u>=N), 8.67 (1H, d, J 14 Hz, N<u>H</u>CH=N); δ_C 8.6 (5-<u>C</u>H_3), 26.7 (C-3), 30.0 (C<u>Me</u>$_3$), 48.9 (C-2), 56.4 (<u>C</u>Me_3), 61.3 (CH_2), 71.7 (CH_2), 116.1 (C-5), 140.8 (NHCH=N), 148.3 (C-4); m/z (+FAB) 227 (M^+, 100%), 582 (3). (-FAB) 127 (M^-, 100%), 481 (5).

2,3-Dihydro-1-[[*N*-(1,1-dimethylethyl)amino]methylene]-4-methoxy-1*H*-pyrrolium iodide **(20a)**

To a stirred solution of formamidine **(9)** (857 mg, 4.00 mmol) in THF (25 ml) at -78°C was added *tert*-butyllithium (1.4M in pentane, 6.29 ml, 8.80 mmol) dropwise. The reaction mixture was allowed to warm gradually to 0°C over 2h. Sodium iodide (1.20 g, 8.00 mmol) was added in one portion followed by a solution of glacial acetic acid (630mg, 0.60 ml, 10.49 mmol) in THF (2 ml) with vigorous stirring. The mixture was allowed to warm to room temperature and stirred for 10 min. Sufficient silica gel slurry in dichloromethane was added to preadsorb the mixture after evaporation under reduced pressure. Chromatography on silica gel using chloroform-methanol (10:1 v/v) as eluant gave a yellow solid which was recrystallized from chloroform-ethyl acetate to give **(20a)** (810 mg, 65%) as colourless needles (3:2 mixture of E/Z isomers (not assigned)), m.p. 200.5-201.5°C (Found: C, 38.60, H, 6.31; N, 8.97%. $C_{10}H_{19}IN_2O$ requires C, 38.72; H, 6.17; N, 9.03%); υ_{max} (nujol mull) 3400 (br), 1660; δ_H 1.54 (9H, s, CMe_3, major isomer), 1.56 (9H, s, CMe_3, minor isomer), 2.78-2.88 (2H, m, 3-H_2), 3.71 (3H, s, OCH_3, minor isomer), 3.88 (3H, s, OCH_3, major isomer), 4.25-4.35 (2H, m, 2-H_2), 6.70 (1H, m, 5-H, minor isomer), 7.62 (1H, m, 5-H, major isomer), 7.77 (1H, d, J 14 Hz, NHC$\underline{H}$=N, major isomer), 8.12 (1H, d, J 14 Hz, NHC$\underline{H}$=N, minor isomer), 8.39 (1H, d, J 14 Hz, N$\underline{H}$CH=N, minor isomer), 8.49 (1H, d, J 14Hz, N$\underline{H}$CH=N, major isomer); δ_C 28.8 and 29.0 (C-3), 30.2 and 30.3 (C$\underline{Me_3}$), 48.7 and 49.8 (C-2), 56.2 and 56.5 ($\underline{C}Me_3$), 58.6 and 60.2 (OCH_3), 104.2 and 104.4 (C-5), 142.5 and 144.6 (NHCH=N), 154.6 and 158.7 (C-4); m/z (+FAB) 183 (M^+, 100%), 275 (2), 365 (1), 493 (3). (-FAB) 127 (M^-, 100%), 219 (55), 311 (23), 437 (33).

2,3-Dihydro-1-[[*N*-(1,1-dimethylethyl)amino]methylene]-4-methoxy-5-methyl-1*H*-pyrrolium iodide (20b)

To a stirred solution of formamidine (9) (1.10 g, 5.14 mmol) in THF (25 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 6.65 ml, 11.31 mmol) dropwise. The resulting yellow solution was allowed to warm gradually to 0°C over 2h, stirred for 30 min at 0°C, then recooled to -78°C. Iodomethane (951 mg, 0.42 ml, 6.70 mmol) was added and the reaction mixture allowed to warm to room temperature. The mixture was then cooled to 0°C and a solution of glacial acetic acid (776mg, 0.74 ml, 12.92 mmol) in THF (5 ml) was added dropwise with vigorous stirring. The reaction mixture was stirred for 10 min at room temperature and then sufficient silica gel slurry in dichloromethane was added to preadsorb the mixture after evaporation under reduced pressure. Chromatography on silica gel using chloroform-methanol (10:1 v/v) as eluant gave an orange crystalline solid which was recrystallized from chloroform-ethyl acetate to give **(20b)** (1.17 g, 70%) as colourless prisms, m.p. 172.5-174°C (Found: C, 40.38; H, 6.62; N, 8.40%. $C_{11}H_{21}IN_2O$ requires C, 40.75; H, 6.53; N, 8.64%); υ_{max} (nujol mull) 3080, 1660 cm^{-1}; δ_H 1.52 (9H, s, CMe_3), 1.91 (3H, t, J 2 Hz, 2-CH_3), 2.89 (2H, m, 3-H_2), 3.65 (3H, s, OCH_3), 4.34 (2H, t, J 7.5 Hz, 2-H_2), 7.35 (1H, d, J 14 Hz, NHC$\underline{H}$=N), 8.38 (1H, d, J 14 Hz, N$\underline{H}$CH=N); δ_C 8.4 (2-CH_3), 25.9 (C-3), 30.0 (C$\underline{Me}_3$), 49.2 (C-2), 56.5 ($\underline{C}Me_3$), 57.6 (OCH_3), 115.3 (C-2), 140.7 (NHCH=N), 148.3 (C-3); m/z (+FAB) 197 (M^+, 100%), 521 (4). (-FAB) 127 (M^-, 100%), 219 (37), 451 (35).

2,3-Dihydro-1-[[*N*-(1,1-dimetylethyl)amino]methylene]-4-methoxy-5-pentyl-1*H*-pyrrolium iodide (20c)

To a stirred suspension of **(20a)** (100 mg, 0.323 mmol) in THF (2 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 0.42 ml, 0.711 mmol) dropwise. The resulting yellow solution was allowed to warm to 0°C over 2h, stirred at 0°C for 30 min, then recooled to -78°C. TMEDA (58 mg, 75 µl, 0.501 mmol) was added followed by 1-bromopentane (54 mg, 44 µl, 0.357 mmol) and the reaction mixture was allowed to warm to room temperature. The mixture was then cooled to 0°C and glacial acetic acid (30 mg, 29 µl, 0.500 mmol) was added. After stirring for 10 min at room temperature, sufficient silica gel slurry in dichloromethane was added to preadsorb the mixture after evaporation at reduced pressure, and chromatography on silica gel using chloroform-methanol (98:2 v/v) as eluant afforded **(20c)** (28 mg, 23%) as a tan gum; υ_{max} (film) 3410 (br), 3200, 1660 cm^{-1}; δ_H 0.88 (3H, t, J 7 Hz, $\underline{CH_3}CH_2$), 1.14-1.42 (6H, m, $CH_3(\underline{CH_2})_3CH_2$), 1.54 (9H, s, CMe_3), 2.33 (2H, t, J 7 Hz, $CH_3(CH_2)_3\underline{CH_2}$), 2.93 (2H, t, J 7 Hz, 3-H_2), 3.68 (3H, s, OCH_3), 4.44 (2H, t, J 7 Hz, 2-H_2), 7.28 (1H, d, J 12 Hz, NHC$\underline{H}$=N), 8.82 (1H, d, J 12 Hz, N$\underline{H}$CH=N); δ_C 13.8 ($\underline{C}H_3CH_2$), 21.9 (CH_2), 22.1 (CH_2), 25.5 (CH_2), 26.0 (CH_2), 30.1 ($C\underline{Me_3}$), 31.2 (CH_2), 49.5 (C-5), 56.5 ($\underline{C}Me_3$), 57.6 ($O\underline{C}H_3$), 118.9 (C-5), 140.4 (NH$\underline{C}$H=N), 148.8 (C-4); m/z (70eV E.I.) 196 (1.5%), 195 (6), 151 (27), 145 (45), 95 (50), 71 (45), 57 (5), 43 (100). Compound **(20c)** was not characterized by elemental analysis or high resolution mass determination.

Further elution with chloroform-methanol (98:2 v/v) afforded starting material **(20a)** (48 mg, 48%).

2,3-Dihydro-1-[[*N*-(1,1-dimethylethyl)amino]methylene]-4-methoxy-5-phenylmethyl-1*H*-pyrrolium iodide (20d)

To a stirred solution of **(9)** (107 mg, 0.499 mmol) in THF (3 ml) at -78°C was added *tert*-butyllithium (1.4M in pentane, 0.78 ml, 1.09 mmol) dropwise. The resulting yellow solution was allowed to warm to 0°C over 2h, stirred at 0°C for 30 min, then recooled to -78°C. Benzyl bromide (110 mg, 77µl, 0.643 mmol) was added and the reaction mixture was allowed to warm to room temperature. The mixture was cooled to 0°C and sodium iodide (0.15 g, 1.00 mmol) was added in one portion followed by glacial acetic acid (60 mg, 57 µl, 1.00 mmol) and the mixture stirred at room temperature for 16h. Sufficient silica gel slurry in dichloromethane was added to preadsorb the mixture after evaporation under reduced pressure, and chromtography using chloroform-methanol (95:5 v/v) as eluant afforded the crude salt as a tan gum; υ_{max} (film) 3400 (br), 1660 cm^{-1}. Recrystallization from ethyl acetate-ether (0°C) gave **(20d)** (28 mg, 14%) as a yellow, microcrystalline solid, m.p. 100-102°C (dec); δ_H 1.24 (9H, s, CMe_3), 3.04 (2H, m, 3-H_2), 3.78 (5H, s, OCH_3 and $PhC\underline{H}_2$), 4.42 (2H, m, 2-H_2), 7.08 (1H, d, J 14 Hz, NHC$\underline{H}$=N), 7.13-7.37 (5H, m, Ph), 9.22 (1H, d, J 14 Hz, N$\underline{H}$CH=N); δ_C 26.2 (CH_2), 28.4 (CH_2), 29.6 ($C\underline{Me}_3$), 48.7 (C-2), 56.1 ($\underline{C}Me_3$), 57.8 (OCH_3), 117.3 (C-5), 127.7 (Ph_{CH}), 129.4 (Ph_{CH}), 134.6 ($Ph_{Cquaternary}$), 141.8 (NHCH=N), 151.0 (C-3); m/z (+FAB) 273 (M^+, 100%), 673 (3.5). (-FAB) 127 (M^-, 100%), 527 (9). Compound **(20d)** did not give satisfactory elemental analysis.

2,3-Dihydro-1-[[*N*-(1,1-dimethylethyl)amino]methylene]-5-(1-hydroxyhexyl)-4-methoxy-1*H*-pyrrolium iodide (20e)

To a stirred solution of formamidine (9) (214 mg, 1.00 mmol) in THF (5 ml) at -78°C was added *tert*-butyllithium (1.4M in pentane, 1.57 ml, 2.20 mmol) dropwise. The resulting yellow solution was allowed to warm to 0°C gradually over 2h, stirred at 0°C for 30 min, then recooled to -78°C. Hexanal (130 mg, 0.156 ml, 1.3 mmol) in THF (1 ml) was added and the reaction mixture allowed to warm to room temperature. The mixture was cooled to 0°C and treated with sodium iodide (225 mg, 1.50 mmol) followed by a solution of glacial acetic acid (210mg, 0.20 ml, 3.50 mmol) in THF (2 ml). The reaction mixture was stirred vigorously for 10 min at room temperature and then sufficient silica gel slurry in dichloromethane was added to preadsorb the mixture after evaporation under reduced pressure. Chromatography on silica gel using chloroform-methanol (95:5 v/v) as eluant afforded **(20e)** (320 mg, 78%) as an amorphous orange solid (3:1 mixture of E/Z isomers (not assigned)); υ_{max} (nujol mull) 3300 (br), 1660 cm^{-1}; δ_H 0.75 (3H, m, $C\underline{H}_3CH_2$), 1.18 (8H, m, $CH(C\underline{H}_2)_4$), 1.33 (9H, s, CMe_3, minor isomer), 1.40 (9H, s, CMe_3, major isomer), 2.55-2.98 (2H, m, 3-H_2), 3.60 (3H, s, OCH_3, major isomer), 3.66 (3H, s, OCH_3, minor isomer), 4.04-4.30 (2H, m, 2-H_2), 4.60-4.89 (1H, m, C$\underline{H}$OH), 8.02 (1H, d, J 14 Hz, NHC$\underline{H}$=N, major isomer), 8.25 (1H, d, J 13 Hz, NHC$\underline{H}$=N, minor isomer), 8.28 (1H, d, J 14 Hz, N$\underline{H}$CH=N, major isomer), 10.02 (1H, d, J 13 Hz, N$\underline{H}$CH=N, minor isomer); m/z (+FAB) 283 (M^+, 100%), 391 92), 409 (1), 693 (1). (-FAB) 127 (M^-, 100%), 305 (5), 537 (10).

The free base was obtained as follows: A portion of the salt **(20e)** was mixed with 1M aqueous potassium hydroxide solution and the mixture was extracted with three portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the free base **(19e)** as a yellow oil in essentially quantitative yield (Found: M^+, 282.2287. $C_{16}H_{30}N_2O_2$ requires 282.2306); m/z (70eV E.I.) 282 (M^+, 6%), 267 (20), 242 (22), 199 (20), 184 (24), 126 (60), 124 (100). (Low eV E.I.) 282 (M^+, 40%), 267 (40), 244 (24), 199 (40), 126 (26), 124 (100).

4,5-Dihydro-1-[[*N*-(1,1-dimethylethyl)imino]methyl]-3-methoxy-α-phenyl-1-*H*-pyrrole -2-methanol **(19f)**

To a stirred solution of formamidine **(9)** (214 mg, 1.00 mmol) in THF (5 ml) at -78°C was added *tert*-butyllithium (1.4M in pentane, 1.57 ml, 2.20 mmol) dropwise. The resulting yellow solution was allowed to warm gradually to 0°C over 2h, stirred at 0°C for 30 min, then recooled to -78°C. Benzaldehyde (138mg, 0.13 ml, 1.3 mmol) was added and the mixture allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (2 ml) was added with vigorous stirring and the mixture was poured onto saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an orange/brown oil. Purification by chromatography on silica gel using ethyl acetate-triethylamine (90:10 v/v) as eluant afforded **(19f)** (251 mg, 87%) as a yellow oil (Found: M^+, 288.1823. $C_{17}H_{24}N_2O_2$ requires 288.1836); υ_{max} (film) 3250 (br), 1620 cm^{-1}; δ_H 1.07 (9H, s, CMe_3), 2.55-2.67 (1H, m, 4-H_A), 2.87-3.02 (1H, m, 4-H_B), 3.67 (3H, s, OCH_3), 3.72-3.79 (2H, m, 5-H_2), 5.83 (1H, s, C<u>H</u>OH), 7.12-7.43 (6H, m, Ph and CH=N), 9.2-10.0 (1H, s, (br), OH); m/z (70eV E.I.) 288 (M^+, 15%), 273 (40), 205 (30), 146 (58), 130 (100), 105 (82).

<u>(αR,4S,5S)- **(27a)** and (αS,4S,5S)-α-[4,5-Dihydro-1-[[*N*-(1,1-dimethylethyl)imino]methyl]-3-methoxy-2-pyrrolyl]-2,2-dimethyl-5-(phenylmethoxy)methyl-1,3-dioxolan-4-methanol **(27b)**</u>

To a stirred solution of formamidine **(9)** (643 mg, 3.00 mmol) in THF (16 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 3.88 ml, 6.6 mmol) dropwise. The resulting yellow solution was allowed to warm to 0°C over 2h, stirred at 0°C for 30 min, then recooled to -78°C. A solution of **(26)**(138,139) (900 mg, 3.60 mmol) in THF (3 ml) was added dropwise and the mixture was allowed to warm to room temperature over 2h. Methanol (5 ml) was added and most of the solvent was removed by evaporation under reduced pressure. The residue was mixed with water (40 ml) and the mixture was extracted with chloroform (4 x 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed by evaporation under reduced pressure to give the crude product as a tan oil (mixture of diastereoisomers) which was chromatographed on silica gel using ethyl acetate-triethylamine (95:5 v/v) as eluant to give **(27a)** (680 mg, 52%) as a straw coloured oil. Adduct **(27a)** was subsequently found to crystallize on storage at -20°C and an analytical sample was obtained by recrystallization from ethyl acetate-ether (-20°C) affording colourless needles, m.p. 109-110°C, $[\alpha]^{25}_D$ +255° (c 0.78 in $CHCl_3$) (Found : C, 66.81; H, 8.41; N, 6.54. $C_{24}H_{36}N_2O_5$ requires C, 66.64; H, 8.39; N, 6.48%); υ_{max} (film) 3300 (br), 1620 cm^{-1}; δ_H 1.09 (9H, s, CMe_3), 1.40 (6H, s, $OCMe_2$), 2.63 (1H, ddd, J 15, 10, 4.5 Hz, 4-H_A), 2.84 (1H, dt, J 15, 10 Hz, 4-H_B), 3.45-3.63 (1H, m), 3.61 (3H, s, OCH_3), 3.65-3.93 (4H, m), 4.42-4.67 (4H, m), 7.18-7.38 (6H, m, Ph and CH=N), 8.80-9.00 (1H, m (br), OH); m/z (70 eV E.I.) 432 (M^+, 6%), 417 (12), 359 (5), 359 (14), 276 (11), 211 (100). (Low eV E.I.) 432 (M^+, 100%), 417 (20), 211 (80).

Further elution using ethyl acetate-triethylamine (95:5 v/v) gave a mixture of isomers (310 mg) which was rechromatographed on silica gel using ethyl acetate-triethylamine (98:2 v/v) as eluant to give a mixed fraction (150 mg, 11%) followed by **(27b)** (103 mg, 8%) as a straw-coloured oil. Adduct **(27b)** was also found to crystallize on storage at -20°C and an analytical sample was obtained by recrystallization from ether-hexane (-20°C) affording colourless needles, m.p. 104-105.5°C, $[\alpha]^{25}{}_D$ -259° (c 0.57 in $CHCl_3$) (Found: C, 66.50; H, 8.42; N, 6.36%. $C_{24}H_{36}N_2O_5$ requires C, 66.64; H, 8.39; N, 6.48%); υ_{max} (film) 3300 br, 1610 cm^{-1}; δ_H 1.16 (9H, s, CMe_3), 1.43 (3H, s, $OCMe_A$), 1.49 (3H, s, $OCMe_B$), 2.30 (1H, ddd, J 15, 10, 5 Hz, 4-H_A), 2.71 (1H, ddd, J 15, 10.5, 9 Hz, 4-H_B), 3.18 (1H, q, J 10 Hz), 3.26-3.41 (2H, m), 3.45-3.61 (1H, m), 3.56 (3H, s, OCH_3), 3.87 (1H, m), 4.01 (1H, t, J 8.5 Hz), 4.45 (1H, d, J 12.5 Hz, PhC$\underline{H}_A$), 4.60-4.70 (1H, m), 4.67 (1H, d, J 12.5 Hz, PhC$\underline{H}_B$), 7,15 (1H, s, CH=N), 7.28-7.37 (5H, m, Ph), 8.81 (1H, s (br), OH); m/z (70 eV E.I.) 432 (M^+, 6%), 417 (10), 349 (18), 276 (8), 211 (77), 91 (100). (Low eV E.I.) 432 (M^+, 100%), 417 (18), 349 (14), 211 (85).

1-[[*N*-(1,1-Dimethylethyl)amino]methylene]-3-methoxy-2-methylpyrrolidinium iodide**(28)**

To a stirred suspension of **(20b)** (975 mg, 3 mmol) in THF (15 ml) at -78°C was added *n*-butyllithium (1.6M in hexane, 2.12 ml, 3.40 mmol) dropwise. The mixture was allowed to warm to room temperature over 30 min. Methanol (1 ml) was added and the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in ethanol (15 ml) and 10% Pd/C (100 mg) was added. The mixture was hydrogenated at atmospheric pressure for 16h after which time the catalyst was removed by filtration through celite and the filtrate evaporated under reduced pressure. The residue was chromatographed on silica gel using chloroform-methanol (95:5 v/v) as eluant to give **(28)** (777 mg, 79%) as an orange solid. An analytical sample was obtained by recrystallization from dichloromethane-ethyl acetate-ether (0°C) giving colourless needles, m.p. 129.5-130.5°C (Found: C, 40.20; H, 7.21; N, 8.57%. $C_{11}H_{23}IN_2O$

requires C, 40.50; H, 7.11; N, 8.58%); υ_{max} (nujol mull) 3440 (br), 3200, 1665 cm^{-1}; δ_H 1.40 (3H, d, J 6.5 Hz, CHC$\underline{H}_3$), 1.58 (9H, s, CMe_3), 2.00-2.30 (2H, m, 4-H_2), 3.36 (3H, s, OCH_3), 3.80-4.10 (3H, m), 4.39 (1H, m), 7.97 (1H,d, J 14 Hz, NHC$\underline{H}$=N), 8.36 (1H, d, J 14 Hz, N$\underline{H}$CH=N); δ_C 14.5 (CH$\underline{C}H_3$), 27.2 (C-4), 30.0 (C$\underline{Me_3}$), 48.8 (C-5), 56.9 ($\underline{C}Me_3$), 57.1 (OCH_3), 61.6 (CH), 79.8 (CH), 148.4 (NHCH=N); m/z (+FAB) 199 (M^+, 100%), 525 (7). (-FAB) 127 (M^-, 100%), 453 (32).

3-Methoxy-2-methylpyrrolidine (29)

Hydrogen iodide salt **(28)** (183 mg, 0.561 mmol) was treated with 1M aqueous potassium hydroxide solution (2 ml) and the mixture was extracted with dichloromethane (3 x 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the free base as an oil in essentially quantitative yield. This material was dissolved in methanol (2.5 ml) and water (1.5 ml) was added followed by potassium hydroxide pellets (0.2 g). The mixture was stirred at 60°C for 3h, cooled, diluted with water (10 ml) and extracted with dichloromethane (2 x 5 ml) followed by chloroform (2 x 5 ml). The combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude amine. Purification by bulb-to-bulb distillation gave **(29)** (42 mg, 65%) as a colourless liquid (b.p. 100-120°C/12mmHg); υ_{max} (film) 3300 (br); δ_H 1.19 (3H, d, J 6.5 Hz, CHC$\underline{H}_3$), 1.88 (2H, m, 4-H_2), 2.80-3.00 (2H, m, 5-H_2), 3.06-3.20 (1H, m, 2-H), 3.30 (3H, s, OCH_3), 3.61 (1H, q, J 3.5 Hz, 3-H) (NH not observed); δ_C 13.71 (CH$\underline{C}H_3$), 31.3 (C-4), 44.3 (C-5), 56.5 (CH), 58.7 (OCH_3), 83.1 (CH); m/z (70eV E.I.) 115 (M^+, 7%), 114 (5), 57 (100), 56 (25). (Low eV E.I.) 115 (M^+, 3%), 89 (22), 57 (100). The molecular ion peak did not give satisfactory high resolution mass determination.

<u>(αR,4S,5S)-*O-tert*-Butyldimethylsilyl-α-[4,5-dihydro-1-[[*N*-(1,1-dimethylethyl)imino]methyl]-3-methoxy-2-pyrrolyl]-2,2-dimethyl-5-(phenylmethoxy)methyl-1,3-dioxolan-4-methanol</u> **(30)**

To a solution of **(27a)** (100 mg, 0.231 mmol) in dichloromethane (1.5 ml) was added *tert*-butyldimethylsilyl chloride (70 mg, 0.464 mmol) followed by DBU (53 mg, 52μl, 0.348 mmol) and the mixture stirred at room temperature for 1.5h. The reaction mixture was diluted with dichloromethane (5 ml) and washed with water (4 ml). The organic layer was collected, the aqueous layer extracted with dichloromethane (5 ml) and the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure. The residue was immediately chromatographed on silica gel using ethyl acetate-triethylamine (90:10 v/v) as eluant to give **(30)** (107 mg, 85%) as a colourless oil (Found : M^+, 546.3451. $C_{30}H_{50}N_2O_5Si$ requires 546.3485); υ_{max} (film) 1760, 1620 cm^{-1}; δ_H 0.10 (6H, s, $SiCH_3$ x 2), 0.85 (9H, s, $SiCMe_3$), 1.18 (9H, s, $NCMe_3$), 1.36 (3H s, $OCMe_A$), 1.42 (3H, s, $OCMe_B$), 2.51-2.57 (2H, m, 4-H_2), 3.57 (3H, s, OCH_3), 3.59 (1H, dd, J 10, 6.5 Hz), 3.72 (1H, dd, J 10, 3Hz), 3.72-3.88 (2H, m), 4.00 (1H, t, J 7 Hz), 4.11-4.21 (1H, m), 4.56 (1H, d, J 12.5 Hz, $PhC\underline{H}_A$), 4.65 (1H, d, J 12.5 Hz, $PhC\underline{H}_B$), 4.78 (1H, d, J 7 Hz), 7.26-7.38 (5H, m, Ph), 8.05 (1H, s, CH=N); m/z (70 eV E.I.) 546 (M^+, 10%), 531 (10), 463 (25), 390 (5), 323 (8), 312 (5), 242 (25), 240 (25), 114 (50), 91 (100). (Low eV E.I.) 546 (M^+, 100), 531 (22), 463 (53), 323 (22), 312 (20), 198 (30).

<u>3,3-Dimethoxy-1-[(4-methylphenyl)sulphonyl]-pyrrolidine</u> **(31)**

To a stirred solution of **(8)** (656 mg, 5.00 mmol) in dichloromethane (20 ml) at 0°C was added pyridine (791 mg, 0.81 ml, 10.00 mmol) followed by toluene-p-sulphonyl chloride (954 mg, 5.00 mmol). The mixture was allowed to warm to room temperature over 30 min and then stirred at room temperature for 16h. The mixture was then diluted with dichloromethane (30 ml) and washed with water (20 ml), followed by 2M aqueous hydrochloric acid (2 x 20 ml). The organic layer was collected and the combined aqueous washings were extracted with dichloromethane (2 x 20 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under redued pressure to give a solid residue which was recrystallized from ethyl acetate-petrol to give **(31)** (581 mg, 41%) as a colourless microcrystalline solid, m.p. 73.5-75°C (Found: C, 54.46; H, 6.69; N, 4.76% $C_{13}H_{19}NO_4S$ requires C 54.72; H, 6.71; N, 4.91%); υ_{max} (nujol mull) 1590, 1450, 1330 cm^{-1}; δ_H 1.95 (2H, t, J 7 Hz, 4-H_2), 2.43 (3H, s, PhC$\underline{H}_3$), 3.09 (6H, s, OCH_3 x 2), 3.31 (2H, s, 2-H_2), 3.35 (2H, t, J 7Hz, 5-H_2), 7.33 (2H, d, J 8 Hz, Ph$\underline{H}_2$), 7.71 (2H, d, J 8 Hz, Ph$\underline{H}_2$); m/z (C.I.) 326 (2%) 284 (2), 254 (100), 130 (50), 98 (40).

Phenylmethyl 3,3-Dimethoxy-1-pyrrolidinecarboxylate (32)

To a stirred suspension of **(8)** (263 mg, 2.00 mmol) in 2M aqueous sodium carbonate solution (4 ml) at 0°C was added benzyl chloroformate (342 mg, 0.286 ml, 2.00 mmol) dropwise. The stirred reaction mixture was allowed to warm to room temperature over 30 min and stirred at that temperature for a further 30 min. The mixture was then extracted with dichloromethane (4 x 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed on silica gel using petrol-ethyl acetate (2:1 v/v) as eluant to give **(32)** (450 mg, 85%) as a colourless oil (Found M^+, 265.1288. $C_{14}H_{19}NO_4$ requires 265.1312); υ_{max} (film) 1690 cm^{-1}; δ_H 2.02 (2H, m, 4-H_2), 3.24 (3H, s, OMe_A), 3.26 (3H, s, OMe_B), 3.45-3.55 (4H, m, 2-H_2 and 5-H_2), 5.13 (2H, s, PhC$\underline{H}_2$), 7.30-7.40 (5H, m, Ph); m/z (70 eV E.I.) 265 (M^+ 6%), 130 (23), 101 (33), 91 (100). (Low eV E.I.) 265 (M^+, 50%), 233 (22), 174 (20), 130 (100), 128 (70), 128 (53).

3,3-Dimethoxy-1-(2-iodobenzoyl)pyrrolidine (33)

To a stirred solution of amine **(8)** (656 mg, 5.00 mmol) in dichloromethane (25 ml) at 0°C was added pyridine (791 mg, 0.81 ml, 10.00 mmol) followed by a solution of

2-iodobenzoyl chloride (1.36 g, 5.00 mmol) in dichloromethane (5 ml) dropwise. The reaction mixture was allowed to warm to room temperature over 30 min and stirred for 16h. The mixture was diluted with dichloromethane (30 ml) and washed with water (20 ml) followed by 2% aqueous hydrochloric acid (2 x 20 ml). The organic layer was collected and the combined aqueous washings extracted with dichloromethane (2 x 20 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using ethyl acetate (100%) as eluant afforded **(33)** (1.72 g, 95%) (Found: M^+, 361.0161. $C_{13}H_{16}INO_3$ requires 361.0175); υ_{max} (film) 1620 cm^{-1}, δ_H 2.05-2.20 (2H, m, 4-H_2), 3.21-3.31 (8H, m), 3.74-3.80 (2H, m), 7.04-7.12 (1H, m, Ph$\underline{H}$), 7.21-7.26 (1H, m, Ph$\underline{H}$), 7.35-7.44 (1H, m, Ph$\underline{H}$), 7.80-7.85 (1H, m, Ph$\underline{H}$); m/z (70 eV E.I.) 361 (M^+, 8%), 231 (35), 101 (100). (C.I.) 362 (MH^+, 57%), 361 (23), 330 (90), 231 (25), 101 (100).

3,3-Dimethoxy-1-(2-iodophenyl)methylpyrrolidine (34)

To a stirred suspension of sodium hydride (80% dispersion in oil, 30 mg, 1.00 mmol) in dimethylformamide (1 ml) at 0°C was added a solution of amine **(8)** (131mg, 1.00mmol) in dimethylformamide (1 ml) dropwise over 5 min. A solution of 2-iodobenzyl chloride (253 mg, 1.00 mmol) in dimethylformamide (1 ml) was then added dropwise and when hydrogen gas evolution had slowed the reaction mixture was allowed to warm to room temperature and stirred for 1h. The solvent was evaporated under reduced pressure (40°C max. water bath temp.), the residue was mixed with water (10 ml) and the mixture extracted with dichloromethane (3 x 5 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (95:5) as eluant afforded **(34)** (230 mg, 66%) as a colourless oil; υ_{max} 2870, 1460, 1440 cm^{-1}; δ_H (250 MHz) 2.15 (2H, t, J 7 Hz, 4-H_2), 2.73-2.86 (4H, m, 2-H_2 and 5-H_2), 3.23 (6H, s, OCH_3 x 2), 3.70 (2H, s(br), Ph$C\underline{H}_2$), 6.87-6.97 (1H, m, Ph$\underline{H}$), 7.26-7.36 (1H, m, Ph$\underline{H}$), 7.43-7.56 (1H, m, Ph$\underline{H}$), 7.77-7.85 (1H, m, Ph$\underline{H}$); m/z (70 eV E.I.) 347 (M^+, 18%), 332 (27), 316 (14), 259 (39), 245 (17), 217 (92), 132 (46). Compound **(34)** was not characterized by elemental analysis or high resolution mass determination.

Iodine-Lithium exchange reaction of **(33)** -- 1-Benzoyl-3,3-dimethoxypyrrolidine **(37)**

To a stirred solution of **(33)** (361 mg, 1.00 mmol) in THF (6 ml) at -78°C was added *n*-butylithium (1.6M in hexane, 0.625 ml, 1.00 mmol) dropwise. The mixture was stirred at -78°C for 5 min then quenched at -78°C with saturated aqueous ammonium chloride solution (5 ml). After warming to room temperature, water (10 ml) was added and the mixture was extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified by chromatography on silica gel using ethyl acetate (100%) as eluant to give **(37)** (33 mg, 14%) as a colourless oil (Found : M^+, 235.1199 $C_{13}H_{17}NO_3$ requires 235.1207); υ_{max} (film) 1625 cm^{-1}; δ_H (250 MHz) 1.95-2.15 (2H, m, 4-H_2), 3.12 (3H, s, OMe_A), 3.23 (3H, s, OMe_B), 3.40-3.55 (2H, m), 3.57-3.85 (2H, m), 7.30-7.58 (5H, Ph); m/z (70 eV E.I.) 235 (M^+, 11%), 204 (8), 105 (82), 101 (100).

N-Benzoylation of **(8)** -- 1-Benzoyl-3,3-dimethoxypyrrolidine **(37)**

To a stirred solution of amine (131 mg, 1.00 mmol) in dichloromethane (5 ml) at 0°C was added pyridine (159 mg, 0.163 ml, 2.01 mmol) followed by a solution of benzoyl chloride (141 mg, 0.116 ml, 1.00 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 16h. The mixture was diluted with dichloromethane (5 ml) and washed with water (5 ml) followed by 2% aqueous hydrochloric acid (2 x 5 ml). The organic layer was collected and the combined aqueous washings were extracted with dichloromethane (2 x 5 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (1:1 v/v) as eluant afforded **(37)** (172mg, 73%) as a colourless oil with spectral characteristics (^1H nmr, mass spectrum) identical to those exhibited by the iodine-lithium exchange reaction product (previous experiment).

Iodine-Lithium exchange reaction of **(33)** --

1-(2-Benzoylbenzoyl)-3,3-dimethoxypyrrolidine **(38)**

To a stirred solution of **(33)** (361 mg, 1.00 mmol) in THF (6 ml) at -78°C was added *n*-butyllithium (1.6M in hexane, 0.625 ml, 1.00 mmol) dropwise. The reaction mixture was stirred at -78°C for 30 min and then iodomethane (185 mg, 81 μl, 1.30 mmol) was added. The mixture was allowed to warm to room temperature over 2h and then quenched with saturated aqueous ammonium chloride solution (3 ml). Water (10 ml) was added and the mixture was extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under dreduced pressure. Purification of the residue by repeated chromatography on silica gel using petrol-ethyl acetate (1:3 v/v-100% ethyl acetate) afforded a major product **(38)** (71 mg, 21%, theoretical yield 50% max.) as a colourless oil; υ_{max} 1765, 1625 cm^{-1}; δ_H 2.15 (2H, t, J 7 Hz, 4-H_2), 3.22 (3H, s, OMe_A), 3.26 (3H, s, OMe_B), 3.35-3.48 (2H, m), 3.50-3.60 (2H, m), 7.35-7.68 (9H, m, aromatics); m/z (70 eV E.I.) 339 (M^+, 2%), 308 (7), 209 (92), 130 (80), 101 (100). (C.I.) 340 (MH^+, 100%), 308 (46), 294 (24), 276 (29). Compound **(38)** was not characterized by elemental analysis or high resolution mass determination.

Iodine-Lithium exchange reaction of **(33)** -- Methylation of the Aryllithium Intermediate **(35)**

To a stirred solution of **(33)** (361 mg, 1.00 mmol) in THF (6 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 1.18 ml, 2.00 mmol) dropwise. The mixture was stirred at -78°C for 30 min and then iodomethane (185 mg, 81 μl, 1.30 mmol) was added. The mixture was allowed to warm to room temperature over 2h and then quenched with saturated aqueous ammonium chloride solution (3 ml). Water (10 ml) was added and the mixture was extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by repeated chromatography on silica gel using ethyl acetate (100%) as eluant gave a colourless oil (120 mg). The ^1H nmr spectrum of this material suggested that the desired product **(39)** was present [δ2.17 (3H, s, $PhC\underline{H}_3$)] in a mixture which also contained **(38)**. The mass spectrum confirmed the presence of a methylated derivative of **(37)** [m/z (70 eV E.I.) 249 (M^+, 18%), 119 (75), 105 (78), 101 (100). (Low eV E.I.) 249 (M^+, 100%), 105 (42), 101 (80)].

Iodine-Lithium exchange reaction of **(34)** -- 3,3-Dimethoxy-1-phenylmethylpyrrolidine **(40)**

To a stirred solution of **(34)** (174 mg, 0.501 mmol) in THF (3 ml) at -78°C was added *n*-butyllithium (1.6M in hexane, 0.32 ml, 0.512 mmol) dropwise. The reaction mixture was allowed to warm to room temperature over 2h and stirred at that temperature for 1h. The mixture was quenched with saturated ammonium chloride solution (2 ml) and water (10 ml) was added. This mixture was extracted with dichloromethane (4 x 5 ml) and the combined extracts dried (K_2CO_3) and evaporated under reduced pressure to give **(40)** (108 mg, 98%) as a colourless oil; υ_{max} 2820, 2800, 1480 cm^{-1}; δ_H (2H, t, J 7 Hz, 4-H_2), 2.72 (4H, m, 2-H_2 and 5-H_2), 3.26 (6H, OCH_3 x 2), 3.66 (2H, s, $PhC\underline{H}_2$), 7.25-7.45 (5H, m, Ph); m/z (70 eV E.I.) 221 (13%), 206 (14), 190 (11), 105 (37), 91 (100). (C.I.) 222 (MH^+, 100%), 207 (10), 190 (8), 132 (6), 110 (22). Compound **(40)** was not characterized by elemental analysis or high resolution mass determination.

1,1-Dimethylethyl 3,3-Dimethoxy-1-pyrrolidinecarboxylate **(41)**

To a stirred solution of amine **(8)** (2.10 g, 16.00 mmol) in dichloromethane (70 ml) was added a solution of di-*tert*-butyldicarbonate (3.5 g, 16.03 mmol) in dichloromethane

(10 ml) dropwise. The mixture was stirred for 4h and then washed with 2% aqueous hydrochloric acid (50 ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (40:60 v/v) afforded **(41)** (3.15 g, 85%) as a colourless oil (Found : M^+, 231.1459. $C_{11}H_{21}NO_4$ requires 231.1469); υ_{max} 1700 cm^{-1}; δ_H (250 MHz) 1.45 (9H, s, CMe_3), 2.02 (2H, t, J 7.5 Hz, 4-H_2), 3.25 (6H, s, OCH_3 x 2), 3.42 (4H, m, 2-H_2 and 5-H_2); m/z (70 eV E.I.) 231 (M^+, 7%), 175 (62), 144 (30), 1010 (55), 57 (100). (Low eV E.I.) 231 (M^+, 30%), 175 (100).

<u>1,1-Dimethylethyl 2,3-Dihydro-4-methoxy-1*H*-pyrrole-1-carboxylate (42)</u>

To a stirred solution of **(41)** (231 mg, 1.00 mmol) in THF (6 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 1.29 ml, 2.20 mmol) dropwise. The mixture was allowed to warm to 0°C over 2h and stirred at 0°C for 1h. Saturated aqueous ammonium chloride solution (2 ml) was then added followed by water (10 ml) and the mixture was extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (8:1 v/v) afforded **(42)** (136 mg, 68%) as a crystalline solid. Trituration with pentane provided analaytically pure material (Found : C, 60.45; H, 8.56; N, 6.85%. $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03%); υ_{max} (nujol mull) 1700, 1660 cm^{-1}; δ_H 1.47, (9H, s, CMe_3), 2.69 (2H, m, 3-H_2), 3.61 (3H, s, OCH_3), 3.70 (2H, m, 2-H_2), 5.76 (0.5H, s, 5-H, (amide resonance)), 5.92 (0.5H, s, 5-H, (amide resonance)); δ_C 28.4 ($C\underline{Me_3}$), 29.3 and 30.2 (C-3), 43.4 and 43.9 (C-2), 57.4 (OCH_3), 79.5 ($\underline{C}Me_3$), 102.3 (C-5), 147.5 (C quaternary) (other Cquaternary not observed); m/z (70 eV E.I.) 199 (M^+, 16%), 174 (5), 143 (80), 128 (29), 84 (54), 57 (100).

Hydrolysis of (42) -- 1,1-Dimethylethyl 3-Oxo-1-pyrrolidinecarboxylate (43)

To a solution of **(42)** (40 mg, 0.200 mmol) in methanol (2 ml) was added 1M aqueous oxalic acid solution (0.75 ml) and the mixture was stirred at room temperature for 16h. Most of the methanol was removed by evaporation at reduced pressure and the residue was mixed with saturated aqueous sodium hydrogen carbonate solution (5 ml) and extracted with dichloromethane (4 x 3 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (6:1 v/v) as eluant gave **(43)** (23 mg, 62%) as a colourless oil (Found : M^+, 185.1046. $C_9H_{15}NO_3$ requires 185.1050); υ_{max} (film) 1765, 1700 cm^{-1} δ_H (250 MHz) 1.50 (9H, s, CMe_3), 2.58 (2H, t, J 7.5 Hz, 4-H_2), 3.70-3.84 (4H, m, 2-H_2 and 5-H_2); δ_C 28.2 ($C\underline{Me}_3$), 36.7 (C-4), 42.1 (C-5), 52.5 (C-2), 80.2 ($\underline{C}Me_3$), 154.2 (O-C=O) (C-3 not observed); m/z (70 eV E.I.) 185 (M^+, 3%), 130 (11), 112 (16), 57 (100). (Low eV E.I.) 185 (M^+, 69%), 130 (95), 57 (100).

Hydrolysis of (41) -- 1,1-Dimethylethyl 3-Oxo-1-pyrrolidinecarboxylate (43)

To a solution of **(41)** (1.73 g, 7.48 mmol) in methanol (80 ml) at 0°C was added 1M aqueous oxalic acid solution (30 ml). The reaction mixture was allowed to warm to room temperature and stirred for 72h. After this time, the mixture was diluted with water (50 ml) and stirred for a further 24h at room temperature. The reaction mixture was then concentrated to half-volume by evaporation under reduced pressure and extracted with dichloromethane (4 x 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (3:1 v/v) as eluant gave **(43)** (1.18 g 85%) as a colouless oil.

General Procedure for the Generation of Organolithium **(44)** from **(41)** -- Preparation of Aldehyde Adducts **(45a-d)**

To a stirred solution of **(41)** (231 mg, 1.00 mmol) in THF (5 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 1.29 ml, 2.20 mmol) dropwise. The resulting yellow solution was warmed to -5 - -10°C (ice/methanol) and stirred within this temperature range for 1.5h. The reaction mixture was then recooled to -78°C and a solution of the aldehyde (1.10 mmol) in THF (1 ml) was added dropwise. The mixture was allowed to warm to room temperature over 30 min and saturated aqueous sodium hydrogen carbonate solution (2 ml) was added. The mixture was diluted with water (20 ml), extracted with ethyl acetate (3 x 10 ml) and the combined extracts were dried (K_2CO_3) and evaporated under reduced pressure. Purification of the residue by rapid chromatography on silica gel using petrol-ethyl acetate (15:1 - 5:1 v/v) as eluant afforded the adduct **(45)**.

i) 1,1-Dimethylethyl 2,3-Dihydro-5-(α-hydroxyphenylmethyl)-4-methoxy-1*H*-pyrrole-1-carboxylate **(45a)**

Isolated as a colourless oil (129 mg, 42%); υ_{max} (film) 3350 (br), 1700, 1660 cm^{-1}; δ_H (DMSO-d_6, 250 MHz) 1.28 (9H, s, CMe_3), 2.60-2.90 (2H, m, 3-H_2), 3.51-3.68 (1H, m, 2-H_A), 3.61 (3H, s, OCH_3), 3.70-3.85 (1H, m, 2-H_B), 5.56-5.67 (1H, m, C<u>H</u>OH), 5.85-6.11 (1H, m(br), OH), 7.21-7.35 (5H, m, Ph); m/z (C.I.) 306 (MH^+, 2%), 305 (3), 290 (36), 288 (28), 232 (44), 218 (41), 190 (100).

ii) <u>1,1-Dimethylethyl</u>
<u>2,3-Dihydro-5-(1-hydroxyhexyl)-4-methoxy-1*H*-pyrrole-1-carboxylate **(45b)**</u>

Isolated as a colourless oil (121 mg, 40%); υ_{max} (film) 3400 (br), 1700, 1635 cm^{-1}; δ_H (DMSO-d_6, 250 MHz) 0.76-0.88 (3H, m, C$\underline{H}_3$CH$_2$), 1.10-1.30 (8H, m, CH$_3$(C$\underline{H}_2$)$_4$), 1.41 (9H, s, CMe$_3$), 2.51-2.82 (2H, m, 3-H$_2$), 3.52 (3H, s, OCH$_3$), 3.52-3.66 (1H, m, 2-H$_A$), 3.68-3.85 (1H, m, 2-H$_B$), 4.27-4.43 (1H, m, C$\underline{H}$OH), 4.97-5.12 (1H, m, OH); m/z (C.I.) 300 (MH$^+$, 4%), 284 (38), 246 (30), 184 (100)

iii) <u>1,1-Dimethylethyl</u>
<u>2,3-Dihydro-5-(1-hydroxy-2-methylpropyl)-4-methoxy-1*H*-pyrrole-1-carboxylate **(45c)**</u>

Isolated as a colourless oil (115 mg, 42%); υ_{max} 3390 (br), 1690, 1650 cm^{-1}. This material was used immediately in the preparation of **(48c)** and **(49c)**.

The adducts **(45a-c)** were not characterized by elemental analysis or high resolution mass determination, but were converted to the corresponding enones **(48/49)** and pyrroles **(52)** (see below), for which analytical data were obtained.

iv) <u>1,1-Dimethylethyl</u>
<u>2,3-Dihydro-5-(α-hydroxy-3-pyridinylmethyl)-4-methoxy-1*H*-pyrrole-1-carboxylate **(45d)**</u>

Isolated as a yellow oil (135 mg, 44%) (Found : M$^+$, 306.1581. $C_{16}H_{22}N_2O_4$ requires 306.1578); υ_{max} (film) 3300 (br), 1690, 1640 cm^{-1}; δ_H 1.33 (9H, s, CMe$_3$), 2.67 (1H, ddd, J 16, 11, 5 Hz, 3-H$_A$), 2.89 (1H, ddd, J 16, 11, 8 Hz, 3-H$_B$), 3.63-3.76 (4H, m, OCH$_3$ and 2-H$_A$), 3.76-3.93 (1H, m, 2-H$_B$), 5.88 (1H, d, J 11 Hz, CHOH), 6.32 (1H, d, J 11 Hz, OH), 7.24 (1H, dd, J 8, 5 Hz, N-CH-CH), 7.83 (1H, d, J 8 Hz, N-CH-CH-CH), 8.44 (1H, d, J 5 Hz, N-CH-CH), 8.51 (1H, s, CH-N-CH-CH); m/z (70 eV E.I.) 306 (M^+, 3%), 250 (94), 233 (2), 232 (2), 206 (20), 191 (30), 131 (21), 107 (100).

1,1-Dimethylethyl 2,3-Dihydro-4-methoxy-5-phenylsulphinyl-1*H*-pyrrole-1-carboxylate **(45e)**

To a stirred solution of **(42)** (199 mg, 1.00 mmol) in THF (5 ml) at -78°C was added *tert*-butyllithium (1.7M in pentane, 0.65 ml, 1.10 mmol) dropwise. The resulting yellow solution was allowed to warm to -5 - -10°C (ice/methanol) and stirred within this temperature range for 1.5h. The solution was then recooled to -78°C and a solution of diphenyl disulphide (240 mg, 1.10 mmol) in THF (2 ml) was added dropwise. The mixture was allowed to warm to room temperature over 30 min and saturated aqueous ammonium chloride solution (2 ml) was then added. The mixture was diluted with water (20 ml), extracted with dichloromethane (3 x 10 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (10:1 v/v) as eluant gave **(45e)** (100 mg, 31%) as a colourless oil. The compound was found to crystallize on storage at -20°C and an analytical sample was obtained by recrystallization from ethyl acetate-hexane (0°C) giving colourless needles, m.p. 94-95°C (Found : C, 59.20; H, 6.55; N 4.26%. $C_{16}H_{21}NO_4S$ requires C, 59.42; H, 6.54; N, 4.33%); υ_{max} (nujol mull) 1750, 1710, 1300 cm^{-1}; δ_H 1.53 (9H, s, CMe_3), 2.06-2.26 (2H, m, 3-H_2), 3.57-3.78 (5H, m, OCH_3 and 2-H_2), 7.31-7.37 (3H, m, PhH_3), 7.45-7.50 (2H, m, PhH_2); m/z (C.I.) 292 (2%), 268 (16), 214 (46), 158 (26), 114 (100).

General Procedure for the Preparation of Enones (48b,c) and (49a-c) from Adducts (45a-c)

To a stirred solution of adduct **(45)** (1.00 mmol) in methanol (6 ml) was added 1M aqueous oxalic acid (3 ml) dropwise. The mixture was stirred at room temperature for 15 min after which time 2M aqueous sodium carbonate (20 ml) was added. The mixture was extracted with ethyl acetate (3 x 10 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (20:1 - 7:1 v/v) as eluant afforded the enones Z-**(48)** and E-**(49)**.

i) (E)-1,1-Dimethylethyl 3-Oxo-2-phenylmethylene-1-pyrrolidinecarboxylate (49a)

Isolated as a crystalline solid which was recrystallized from ethanol to give colourless prisms (235 mg, 86%), m.p. 114.5-115.5°C (Found : C, 70.60; H, 7.04; N, 5.02%. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.00; N, 5.12%); υ_{max} (nujol mull) 1725, 1700, 1620 cm^{-1}; δ_H 1.12 (9H, s, CMe_3), 2.62 (2H, t, J 7 Hz, 4-H_2), 3.93 (2H, t, J 7 Hz, 5-H_2), 6.69 (1H, s, PhC$\underline{H}$=C), 7.28-7.43 (5H, m, Ph); δ_C 38.3 (C$\underline{Me_3}$), 44.8 (C-4), 54.1 (C-5), 91.9 ($\underline{C}Me_3$), 125.9 (Ph$\underline{C}$H=C), 131.0 (C-2), 138.8 (Ph_{CH}), 139.2 (Ph_{CH}), 140.9 (Ph_{CH}), 142.5 ($Ph_{Cquaternary}$), 146.0 (O-C=O), 212.3 (C-3); m/z (Low eV E.I.) 273 (M^+, 56%), 217 (100), 173 (50).

ii) (Z)-1,1-Dimethylethyl 3-Oxo-2-hexylidene-1-pyrrolidinecarboxylate (48b)

First eluted isomer isolated as a colourless oil (89 mg, 33%) (Found : M^+, 267.1830. $C_{15}H_{25}NO_3$ requires 267.1833); υ_{max} (film) 1760, 1690, 1610 cm^{-1}; δ_H (DMSO-d_6, 250 MHz), 0.84 (3H, t, J 7 Hz, $\underline{CH_3}CH_2$), 1.13-1.31 (6H, m, $CH_3(\underline{CH_2})_3$), 1.45 (9H, s, CMe_3), 2.10-2.28 (2H, m, 4-H_2), 2.50-2.66 (2H, m,

$C\underline{H}_2CH=C$), 3.6 (2H, t, J 7 Hz, 5-H_2), 6.37-6.60 (1H, m (br), CH=C); m/z (70 eV E.I.) 267 (M^+, 2%), 243 (1), 211 (15), 57 (100). (Low eV E.I.) 267 (M^+, 36%), 211 (100), 57 (62).

iii) (E)-1,1-Dimethylethyl 3-Oxo-2-hexylidene-1-pyrrolidinecarboxylate (49b)

Second eluted isomer isolated as a colourless oil (67 mg, 25%) (Found : M^+, 267.1844. $C_{15}H_{25}NO_3$ requires 267.1833); υ_{max} (film) 1730, 1700, 1640 cm^{-1}; δ_H (DMSO-d_6, 250 MHz) 0.85 (3H, t, J7Hz, $C\underline{H}_3CH_2$), 1.15-1.32 (6H, m, $CH_3(C\underline{H}_2)_3$), 1.46 (9H, s, CMe_3), 2.05-2.20 (2H, m, $C\underline{H}_2CH=C$), 2.51 (2H, t, J 7 Hz, 4-H_2), 3.64 (2H, t, J 7 Hz, 5-H_2), 5.77 (1H, t, J 7 Hz, CH=C). δ_H ($CDCl_3$, 270 MHz) 0.91 (3H, m, $C\underline{H}_3CH_2$), 1.21-1.39 (6H, m, $CH_3(C\underline{H}_2)_3$), 1.52 (9H, s, CMe_3), 2.22 (2H, q, J 7 Hz, $C\underline{H}_2CH=C$), 2.51 (2H, t, J 7 Hz, 4-H_2), 3.87 (2H, t, J 7 Hz, 5-H_2), 6.06 (1H, t, J 7 Hz, CH=C); δ_C 14.0 ($\underline{C}H_3CH_2$), 22.4 (CH_2), 28.3 ($C\underline{Me}_3$), 28.4 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 34.6 (CH_2), 43.3 (CH_2), 81.4 ($\underline{C}Me_3$), 122.7 ($\underline{C}H=C$), 132.9 (C-2), 152.6 (O-C=O), 200.1 (C-3); m/z (70 eV E.I.) 267 (M^+, 3%), 211 (28), 141 (20), 57 (100). (Low eV E.I.) 267 (M^+, 13%), 211 (100), 139 (12), 57 (60).

iv) (Z)-1,1-Dimethylethyl
3-Oxo-2-(2-Methylpropylidene)-1-pyrrolidinecarboxylate (48c)

First eluted isomer isolated as a colourless oil (39 mg, 16%). The oil crystallized on storage at -20°C giving colourless needles, m.p. 56-59°C (dec.) (Found : C, 65.40; H, 9.15; N, 5.72%. $C_{13}H_{21}NO_3$ requires C, 65.24; H, 8.84; N, 5.85%); υ_{max} (film) 1730, 1690, 1610 cm^{-1}; δ_H (DMSO-d_6, 270 MHz) 0.95 (6H, d, J 7 Hz, $CH\underline{Me}_2$), 1.46 (9H, s, $C\underline{Me}_3$), 2.55 (2H, t, 7.5 Hz, 4-H_2), 3.63-3.79 (3H, m, $C\underline{H}Me_2$ and 5-H_2), 6.23-6.51 (1H, m (br), CH=C). δ_H ($CDCl_3$, 270 MHz) 1.03 (6H, d, J 7 Hz, $CH\underline{Me}_2$), 1.53 (9H, s, CMe_3), 2.54 (2H, t, J 7.5 Hz, 4-H_2), 3.67-3.85 (1H, m, C<u>H</u>Me_2), 3.78 (2H, t, J 7.5 Hz, 5-H_2), 6.30-6.68 (1H, m(br), CH=C); δ_C (DMSO-d_6) 23.3 (CH<u>Me</u>$_2$), 23.8 (<u>C</u>HMe_2), 27.9 (C<u>Me</u>$_3$), 34.2 (C-4), 42.0 (C-5), 80.3 (<u>C</u>Me_3), 128.9 (<u>C</u>H=C), 130.8 (C-2), 152.2 (O-C=O), 200.8 (C-3); m/z (Low eV E.I.) 239 (M^+, 39%), 184 (29), 183 (100).

v) <u>(E)-1,1-Dimethylethyl 3-Oxo-2-(2-Methylpropylidene)-1-pyrrolidinonecarboxylate (49c)</u>

Second eluted isomer isolated as a colourless oil (53 mg, 22%) (Found : M^+, 239.1510. $C_{13}H_{21}NO_3$ requires 239.1520); υ_{max} (film) 1765, 1700 cm^{-1}; δ_H 1.03 (6H, d, J 7 Hz, CH<u>Me</u>$_2$), 1.53 (9H, s, CMe_3), 2.50 (2H, t, J 7.5 Hz, 4-H_2), 2.89 (1H, dhept, J 9.5, 7 Hz, C<u>H</u>Me_2), 3.85 (2H, t, J 7.5 Hz, 5-H_2), 5.88 (1H, d, J 9.5 Hz, CH=C); δ_C 22.3 (CH<u>Me</u>$_2$), 27.2 (<u>C</u>HMe_2), 28.2 (C<u>Me</u>$_3$), 34.2 (C-4), 43.6 (C-5), 80.8 (<u>C</u>Me_3), 125.8 (<u>C</u>H=C), 131.3 (C-2), 152.1 (O-C=O), 200.7 (C-3); m/z (70 eV E.I.) 239 (M^+, 1%), 183 (31), 124 (16), 57 (100).

<u>General Procedure for the Preparation of Pyrroles **(52a-c)** from Adducts **(45a-c)**</u>

To a solution of adduct **(45)** (0.50 mmol) in dichloromethane (3 ml) was added *tert*-butyldimethylsilyl chloride (5 mg) and the mixture was stirred at room temperature for 15-45 min. The mixture was diluted with dichloromethane (10 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (5 ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (20:1 - 15:1 v/v) as eluant afforded the pyrolle **(52)**.

i) 1,1-Dimethylethyl 3-Methoxy-2-phenylmethyl-1*H*-pyrrole-1-carboxylate (52a)

Isolated as a colourless solid (72 mg, 50%) which was recrystallized from aqueous methanol to give colourless plates, m.p. 70-71°C (Found : C, 71.00; H, 7.39; N, 4.74%. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.37; N, 4.87%); υ_{max} (nujol mull) 1720, 1620 cm^{-1}; δ_H (DMSO-d_6) 1.32 (9H, s, CMe_3), 3.70 (3H, s, OCH_3), 4.10 (2H, s, $PhC\underline{H_2}$), 6.31 (1H, d, J 4 Hz, 4-H), 6.98 (2H, d, J 7 Hz, $Ph\underline{H_2}$), 7.10-7.18 (1H, m, $Ph\underline{H}$), 7.15 (1H, d, J 4 Hz, 5-H), 7.24 (2H, t, J 7 Hz, $Ph\underline{H_2}$); m/z (Low eV E.I.) 287 (M^+, 69%), 232 (15), 231 (100), 187 (21).

ii) 1,1-Dimethylethyl 2-Hexyl-3-methoxy-1*H*-pyrrole-1-carboxylate (52b)

Isolated as a colourless oil (100 mg, 71%) (Found : M^+, 281.1983. $C_{16}H_{27}NO_3$ requires 281.1989); υ_{max} (film) 1730, 1600 cm^{-1}; δ_H (DMSO-d_6) 0.83 (3H, t, J 6.5 Hz, $C\underline{H_3}CH_2$), 1.17-1.28 (6H, m, $CH_3(C\underline{H_2})_3$), 1.32-1.48 (2H, m, $CH_3(CH_2)_3C\underline{H_2}$), 1.51 (9H, s, CMe_3), 2.65 (2H, t, J 7.5 Hz), 3.63 (3H, s, OCH_3), 6.17 (1H, d, J 3.5 Hz, 4-H), 7.01 (1H, d, J 3.5 Hz, 5-H); δ_C (DMSO-d_6) 13.8 ($\underline{C}H_3CH_2$), 22.0 (CH_2), 23.7 (CH_2), 27.5 ($C\underline{Me_3}$), 28.3 (CH_2), 29.5 (CH_2), 31.0 (CH_2), 58.3 (OCH_3), 83.2 ($\underline{C}Me_3$), 101.5 (C-4), 117.5 (C-2 and C-5), 146.4 (Cquaternary), 149.0 (Cquaternary); m/z (70 eV E.I.) 281 (M^+, 5%), 225 (34), 181 (10), 154 (57), 110 (92), 57 (100).

iii) 1,1-Dimethylethyl 3-Methoxy-2-(2-methylpropyl)-1*H*-1-pyrrole-1-carboylate (52c)

Isolated as a colourless oil (51 mg, 40%) (Found : M^+, 253.1690. $C_{14}H_{23}NO_3$ requires 253.1676); υ_{max} (film) 1730, 1600 cm^{-1}; δ_H 0.87 (6H, d, J 7 Hz, $CH\underline{Me_2}$), 1.58 (9H, s, $C\underline{Me_3}$), 1.85 (1H, m, J 7 Hz, $C\underline{H}Me_2$), 2.62 (2H, d, J 7 Hz, $C\underline{H_2}CHMe_2$), 3.72 (3H, s, OCH_3), 6.05 (1H, d, J 4 Hz, 4-H), 7.07 (1H, d, J 4 Hz, 5-H); δ_C 22.3 (CH<u>Me$_2$</u>), 28.0 (C<u>Me$_3$</u>), 28.6 (<u>C</u>HMe$_2$), 33.1 (CH_2), 58.6 (OCH_3), 83.2 (<u>C</u>Me$_3$), 100.5 (C-4), 117.8 (C-5), 117.9 (C-2), 147.2 (Cquaternary), 149.5 (Cquaternary); (70 eV E.I.) 253 (M^+, 11%), 197 (37), 154 (93), 110 (100), 57 (97).

<u>2,3-Dihydro-4-methoxy-5-phenylsulfinyl-1*H*-pyrrole (55)</u>

To a solution of **(45e)** (40 mg, 0.124 mmol) in methanol (3 ml) was added 1M aqueous oxalic acid (1.5 ml) and the mixture was heated at 60°C for 16h. After cooling, the mixture was diluted with water (10 ml) and extracted with dichloromethane (5 x 5 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure and the residue was chromatographed on silica gel using ethyl acetate (100%) as eluant to give **(55)** (14 mg, 50%) as a colourless oil. Prolonged storage at -20°C initiated crystallization of the compound and an analytical sample was obtained by recrystallization from ethyl acetate-hexane affording colourless needles, m.p. 87-88.5°C (Found : C, 59.20; H, 5.96; N, 6.29%. $C_{11}H_{13}NO_2S$ requires C, 59.17; H, 5.87; N, 6.27%); υ_{max} (film) 3260 (br), 1690 cm^{-1}; δ_H 2.20-2.41 (2H, m, 3-H_2), 3.27-3.43 (2H, m, 2-H_2), 3.69 (3H, s, OCH_3), 6.23 (1H, s(br), NH), 7.28-7.36 (3H, m, Ph<u>H$_3$</u>), 7.46-7.55 (2H, m, Ph<u>H$_2$</u>); m/z (70 eV E.I.) 223 (M^+, 1%), 114 (100), 57 (100). (C.I.) 224 (MH^+, 4%), 223 (1), 92 (15), 114 (100).

<u>Ethyl 2,3-Dihydro-4-methoxy-1*H*-pyrrole-1-carboxylate (56)</u>

To a solution of diisopropylamine (668 mg, 0.925 ml, 6.60 mmol) in THF (3 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 3.94 ml, 6.3 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and a solution of **(7)** (610 mg, 3.00 mmol) in THF (5 ml) was then added dropwise. The mixture was allowed to warm to room temperature, stirred for 30 min, then recooled to 0°C. Saturated aqueous ammonium chloride solution (5 ml) was added and the mixture was poured onto water

(30ml) and extracted with dichloromethane (4 x 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (10:1 v/v) as eluant afforded **(56)** (325 mg, 63%) as a colourless oil; υ_{max} (film) 1700, 1670 cm^{-1}; δ_H (DMSO-d_6) 1.19 (3H, t, J 7 Hz, $\underline{CH_3}CH_2$), 2.65 (2H, m, 3-H_2), 3.57 (3H, s, OCH_3), 3.65 (2H, m, 2-H_2), 4.05 (2H, q, J 7 Hz, $CH_3\underline{CH_2}$), 5.91 (1H, m, 5-H); δ_C (DMSO-d_6) 14.7 ($\underline{C}H_3CH_2$), 28.7 and 29.6 (C-3), 43.5 (C-2), 57.4 (OCH_3), 60.4 ($CH_3\underline{C}H_2$), 101.7 and 102.0 (C-5), 147.9 (Cquaternary), 152.5 (Cquaternary); m/z (C.I.) 172 (MH^+, 28%), 159 (30), 156 (100). Compound **(56)** was not characterized by elemental analysis or high resolution mass determination.

Hydrolysis of (56) -- Ethyl 3-Oxo-1-pyrrolidinecarboxylate (5)

To a solution of **(56)** (91 mg, 0.532 mmol) in p-dioxane (2 ml) was added 1M aqueous oxalic acid (1 ml) and the mixture was stirred at room temperature for 16h. The mixture was then concentrated by evaporation under reduced pressure until the oxalic acid began to crystallize (approx. half x original volume). This residue was poured onto saturated aqueous sodium hydrogen carbonate solution (10 ml) and extracted with dichloromethane (4 x 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **(5)**[(114)] (57 mg, 68%) as a straw coloured oil; υ_{max} (film) 1755, 1695 cm^{-1}; δ_H 1.29 (3H, t, J 7 Hz, $\underline{CH_3}CH_2$), 2.61 (2H, t, J 7.5 Hz, 4-H_2), 3.80 (2H, s, 2-H_2), 3.83 (2H, t, J 7.5 Hz, 5-H_2), 4.19 (2H, q, J 7 Hz, $CH_3\underline{CH_2}$).

Deuteration of Organolithium (57) -- Ethyl
5-Deuterio-2,3-dihydro-4-methoxy-1*H*-pyrrole-1-carboxylate (59)

To a solution of diisopropylamine (101 mg, 0.14 ml, 1.00 mmol) in THF (1 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 0.625 ml, 1.00 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and a solution of **(56)** (171 mg, 1.00

mmol) in THF (2 ml) was then added dropwise. The mixture was stirred at 0°C for 30 min and then cooled to -78°C. *n*-Butyllithium (1.6M in hexane, 0.625 ml, 1.00 mmol) was added dropwise over 5 min and the reaction mixture was then allowed to warm to room temperature over 30 min and stirred for 1h. D_2O (1 ml) was added and the mixture was stirred vigorously for 5 min and then poured onto saturated aqueous ammonium chloride solution (10 ml) and extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of **(59)** and **(56)** (150 mg, 9:1 **(59)**:**(56)** (^{1}H nmr), 78% of **(59)** (86% accounting for unreacted **(56)**)) as an orange oil; δ_H (DMSO-d_6) 1.13-1.25 (3H, m, C<u>H</u>$_3$CH$_2$ **(59)** and **(56)**), 2.65 (2H, m, 3-H_2 **(59)** and **(56)**), 3.57 (3H, s, OCH_3 **(59)** and **(56)**), 3.65 (2H, m, 2-H_2 **(59)** and **(56)**), 4.05 (2H, q, J 7 Hz, CH$_3$C<u>H</u>$_2$ **(59)** and **(56)**), 5.91 (1H, m, 5-H **(56)**).

<u>Methylation of Organolithium **(57)** -- Ethyl 2,3-Dihydro-4-methoxy-5-methyl-1*H*-pyrrole-1-carboxylate **(58)**</u>

To a solution of diisopropylamine (202 mg, 0.28 ml, 2.00 mmol) in THF (2 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 1.25 ml, 2.00 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and a solution of **(56)** (342 mg, 2.00 mmol) in THF (4 ml) was then added dropwise. The mixture was stirred at 0°C for 30 min and then cooled to -78°C. *n*-Butyllithium (1.6M in hexane, 1.25 ml, 2.00 mmol) was added dropwise over 10 min and the reaction mixture was then allowed to warm to room temperature over 30 min and stirred for 1h. Iodomethane (426 mg, 0.19 ml, 3.00 mmol) was added and the mixture was stirred for 5 min and then quenched with saturated aqueous ammonium chloride solution (3 ml). The mixture was poured onto water (10 ml) and extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of **(58)** and **(56)** (325mg, 4:1 **(58)**:**(56)** (^{1}H nmr), 71% of **(58)** (87% accounting for unreacted **(56)**)) as an orange oil; δ_H (DMSO-d_6) 1.14-1.32 (3H, m, C<u>H</u>$_3$CH$_2$ **(58)** and **(56)**), 1.93

(3H, t, J 2.5 Hz, 2-CH_3 **(58)**), 2.55-2.69 (2H, m, 3-H_2 **(58)** and **(56)**), 3.50 (3H, s, OCH_3 **(58)**), 3.57 (3H, s, OCH_3 **(56)**), 3.63-3.71 (2H, m, 2-H_2 **(58)** and **(56)**), 3.98-4.10 (2H, m, $CH_3\underline{CH_2}$ **(58)** and **(56)**), 5.91 (1H, m, 5-H **(56)**).

Ethyl 2,3-Dihydro-5-(α-hydroxyphenylmethyl)-4-methoxy-1*H*-pyrrole- 1-carboxylate **(60)**

To a solution of diisopropylamine (111 mg, 0.154 ml, 1.10 mmol) in THF (1 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 0.688 ml, 1.10 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and a solution of **(56)** (171 mg, 1.00 mmol) in THF (2 ml) was then added dropwise. The mixture was stirred at 0°C for 30 min and then cooled to -78°C. *n*-Butyllithium (1.6M in hexane, 0.688 ml, 1.10 mmol) was added dropwise over 5 min and the reaction mixture was then allowed to warm to room temperature over 30 min and stirred for 1h. Benzaldehyde (117 mg, 0.11 ml, 1.10 mmol) was added and the mixture was stirred for 30 min and then quenched with saturated aqueous ammonium chloride solution (3 ml). The mixture was poured onto water (10 ml) and extracted with dichloromethane (5 x 10 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure and the residue was chromatographed on silica gel using petrol-ethyl acetate (1:1 - 5:1 v/v) as eluant to give first-eluted **(56)** (50 mg) followed by second-eluted **(60)** (189 mg, 68% (96% accounting for recovered **(56)**)) as a colourless oil which was used immediately in the preparation of enone **(61)** and pyrrole **(62)** as described below:

(i) (E)-Ethyl 3-Oxo-2-Phenylmethylene-1-pyrrolidinonecarboxylate **(61)**

To a solution of **(60)** (84 mg, 0.302 mmol) in methanol (3 ml) was added 1M aqueous oxalic acid (1.5 ml) and the mixture was stirred at room temperature for 30 min. The reaction mixture was then concentrated to approximately half-volume by evaporation under reduced pressure, diluted with water (10 ml), and extracted with dichloromethane (4 x 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **(61)** (65 mg, 88%) as a crystalline solid which was recrystallized from ethyl acetate-petrol to give colourless plates, m.p. 106-108°C (Found : C, 68.70; H, 6.12; N, 5.56%. $C_{14}H_{15}NO_3$ requires C, 68.70; H, 6.16; N, 5.71%); υ_{max} (nujol mull) 1680 cm^{-1}; δ_H (DMSO-d_6) 0.75 (3H, m(br), $C\underline{H}_3CH_2$), 2.65 (2H, t, J 7 Hz, 4-H_2), 3.85 (2H, m, $CH_3C\underline{H}_2$), 3.97 (2H, t, J 7 Hz, 5-H_2), 6.72 (1H, s, PhC$\underline{H}$=C), 7.28-7.38 (5H, m, Ph); m/z (70 eV E.I.) 245 (M^+, 80%), 173 (13), 130 (100), 117 (34), 116 (23).

(ii) Ethyl 3-Methoxy-2-phenylmethyl-1*H*-pyrrole-1-carboxylate (62)

To a solution of **(60)** (100 mg, 0.361 mmol)in dichloromethane (1.5 ml) was added trimethylsilyl chloride (0.02 ml) and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with dichloromethane (10 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (5 ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (5:1 v/v) as eluant afforded **(62)** (18 mg, 19%) as a colourless oil (Found : M^+ 259.1204. $C_{15}H_{17}NO_3$ requires 259.1207); υ_{max} (film) 1730, 1600 cm^{-1}; δ_H 1.20 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 3.79 (3H, s, OCH_3), 4.19 (2H, s, $PhC\underline{H}_2$), 4.22 (2H, q, J 7 Hz, $CH_3C\underline{H}_2$), 6.15 (1H, d, J 4 Hz, 4-H), 7.08-7.30 (6H, m, Ph and 5-H); δ_C 14.0 ($\underline{C}H_3CH_2$), 29.7 ($Ph\underline{C}H_2$), 58.8 (OCH_3), 62.9 ($CH_3\underline{C}H_2$), 101.5 (C-4), 116.4 (C-2), 118.3 (C-5), 125.6 (Ph_{CH}), 127.8 (Ph_{CH}), 128.1 (Ph_{CH}), 140.8 ($Ph_{Cquaternary}$), 147.7 (Cquaternary) 150.6 (Cquaternary) ; m/z (70 eV E.I.) 259 (M^+, 100%), 186 (24), 110 (33).

Hydrolysis of the 4:1 mixture of (58):(56) -- Ethyl 3-Methoxy-4-oxopentylcarbamate (64)

The mixture of **(58)**:**(56)** (319 mg, (1.41 mmol of **(58)**) was dissolved in methanol (4 ml) and the solution was treated with 1M aqueous oxalic acid (2 ml). The resulting mixture was stirred at room temperature for 1h, poured onto saturated aqueous sodium chloride solution (15 ml) and extracted with dichloromethane (5 x 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel using petrol-ethyl acetate (10:1, 5:1, 4:1 and finally 3:1 v/v) as eluant to give **(64)** (129 mg, 45% from **(58)** (32% in two steps from **(56)**) as a straw-coloured oil; υ_{max} (film) 3320 (br), 1700 (br), 1525 cm^{-1}; δ_H 1.24 (3H, t, J 7 Hz, C$\underline{H}_3$CH$_2$), 1.83 (2H, m, C$\underline{H}_2$CH$_2$NH), 2.18 (3H, s, CH$_3$C=O), 3.16-3.45 (2H, m, C$\underline{H}_2$NH), 3.39 (3H, s, OCH$_3$), 3.67 (1H, dd, J 8, 5 Hz, C$\underline{H}$OCH$_3$), 4.11 (2H, q, J 7 Hz, CH$_3$C$\underline{H}_2$), 4.70-5.03 (1H, m(br), NH); δ_C 14.6 ($\underline{C}$H$_3$CH$_2$), 25.3 ($\underline{C}$H$_3$C=O), 3.17 ($\underline{C}$H$_2$CH$_2$NH), 37.5 (CH$_2$NH), 58.2 (OCH$_3$), 60.7 (CH$_3\underline{C}$H$_2$), 85.5 ($\underline{C}$HOCH$_3$), 156.6 (O-C=O), 210.7 (CH$_3\underline{C}$=O); m/z (C.I.) 204 (MH$^+$, 100%), 186 (56), 172 (16), 160 (84), 158 (71), 115 (33), 102 (62), 71 (41). Compound **(64)** was not characterized by elemental analysis or high resolution mass determination.

Ethyl 2,3-Dihydro-4-(2-hydroxyethoxy)-1*H*-pyrrole-1-carboxylate (66)

To a solution of diisopropylamine (576 mg, 0.80 ml, 5.69 mmol) in THF (1 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 3.42 ml, 5.47 mmol) dropwise. The mixture was stirred at 0°C for 10 min and a solution of **(6)** (459 mg, 2.28 mmol) in THF (4 ml) was then added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then recooled to 0°C. Saturated aqueous ammonium chloride solution (3 ml) was added and the mixture was poured onto water (15 ml) and extracted with dichloromethane (4 x 15 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatograpy on silica gel using petrol-ethyl acetate (1:1 v/v) as eluant afforded **(66)** (374 mg, 81%) as a colourless oil. The compound crystallized on storage at -20°C and trituration with petrol provided the analytically pure microcrystalline solid, m.p. 79-81°C (Found : C, 53.60; H, 7.62; N, 6.86%. $C_9H_{15}NO_4$ requires C, 53.72; H, 7.51; N, 6.96%) (Found : M^+ 201.1002. $C_9H_{15}NO_4$ requires 201.0999); υ_{max} (film) 3410 (br), 1680, 1650 cm^{-1}; δ_H (DMSO-d_6) 1.18 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 2.66 (2H, m, 3-H_2), 3.56-3.71 (4H, m, 2-H_2 and $C\underline{H}_2OH$), 3.73 (2H, t, J 5 Hz, $C\underline{H}_2CH_2OH$), 4.04 (2H, q, J 7 Hz, $CH_3C\underline{H}_2$), 4.80 (1H, t, J 5 Hz, OH), 5.89 (1H, s, 5-H); δ_C (DMSO-d_6) 14.8 ($\underline{C}H_3CH_2$), 28.9 and 29.9 (C-3), 43.4 and 43.4 (C-2), 59.4 (CH_2), 60.5 (CH_2), 72.0 (CH_2), 101.9 and 102.2 (C-5), 146.8 (Cquaternary), 152.0 (Cquaternary); m/z (70 eV E.I.) 201 (M^+, 33%), 157 (21), 156 (26), 84 (100).

<u>Ethyl 6,10-Dioxa-2-azaspiro[5.4]decane-2-carboxylate (70)</u>

To a solution of (5) (629 mg, 4.00 mmol) in benzene (60 ml) was added propane-1,3-diol (548 mg, 0.52 ml, 7.20 mmol) and toluene-p-sulphonic acid (15 mg) and the mixture was heated at reflux with azeotropic removal of water for 16h (Dean-Stark). After cooling, the solvent was removed by evaporation under reduced pressure and the residue was dissolved in dichloromethane (40 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (20 ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (3:1 v/v) as eluant afforded **(70)** (803 mg, 93%) as a colourless oil (Found : M^+, 215.1154. $C_{10}H_{17}NO_4$ requires 215.1156); υ_{max} (film) 1680 cm^{-1}; δ_H 1.26 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 1.50-1.96 (2H, m(br), 8-H_2), 2.13 (2H, t, J 7.5 Hz, 4-H_2), 3.40-3.52 (2H, m(br), 3-H_2), 3.52-3.70 (2H, s(br), 1-H_2), 3.82-4.01 (4H, m, 7-H_2 and 9-H_2), 4.14 (2H, q, J 7 Hz, $CH_3C\underline{H}_2$); m/z (70 eV E.I.) 215 (M^+, 57%), 186 (43), 142 (25), 113 (100).

Ethyl 2,3-Dihydro-4-(3-hydroxypropoxy)-1*H*-pyrrole-1-carboxylate **(71)**

To a solution of diisopropylamine (332 mg, 0.46 ml, 3.28 mmol) in THF (1 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 1.96 ml, 3.13 mmol) dropwise. The mixture was stirred at 0°C for 10 min and a solution of **(70)** (320 mg, 1.49 mmol) in THF (4 ml) was then added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then recooled to 0°C. Saturated aqueous ammonium chloride solution (3 ml) was added and the mixture was poured onto water (15 ml) and extracted with dichloromethane (4 x 15 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using ethyl acetate (100%) as eluant afforded **(71)** (270 mg, 84%) as a colourless oil (Found : M^+, 215.1149. $C_{10}H_{17}NO_4$ requires 215.1156); υ_{max} (film) 3420 (br), 1680, 1650 cm^{-1}; δ_H (DMSO-d_6) 1.18 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 1.76 (2H, quin, J 6 Hz, $C\underline{H}_2CH_2OH$), 2.64 (2H, m, 3-H_2), 3.47 (2H, m, $C\underline{H}_2OH$), 3.63 (2H, m, 2-H_2), 3.78 (2H, t, J 6 Hz, $C\underline{H}_2CH_2CH_2OH$), 4.04 (2H, q, J 7 Hz, $CH_3C\underline{H}_2$), 4.50 (1H, m, OH), 5.87 (1H, s, 5-H); δ_C(DMSO-d_6) 14.8 ($\underline{C}H_3CH_2$), 28.9 and 29.9 (C-3), 32.0 ($\underline{C}H_2CH_2OH$), 43.2 and 43.4 (C-2), 57.3 (CH_2), 60.5 (CH_2), 67.1 (CH_2), 101.8 and 102.1 (C-5), 146.8 (Cquaternary) (other Cquaternary not observed); m/z (70 eV E.I.) 215 (M^+, 28%), 157 (28), 156 (30), 84 (100).

Reaction of Dianion **(72)** with Electrophiles -- Preparation of Adducts **(74a-h)**

General Procedure A (HMPA as cosolvent)

To a solution of diisopropylamine (223 mg, 0.309 ml, 2.20 mmol) in THF (1 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 1.31 ml, 2.10 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and then cooled to -78°C. A solution of **(4)** (229 mg, 1.00 mmol) in THF (4 ml) was added dropwise. The resulting reddish-brown suspension was dissolved by adding HMPA (0.3 ml) and the red solution thus formed was stirred at -78°C for 1h. After this time, the neat electrophile (1.00 mmol) was added and the reaction mixture was stirred at -78°C for 20 min, then allowed to warm to 0°C over 30 min. 2M aqueous hydrochloric acid (3 ml) was added at 0°C and the mixture was stirred vigorously for 5 min then poured onto water (20 ml) and extracted with ether (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (9:1 - 3:1 v/v) as eluant afforded the adduct **(74)**.

General procedure **B** (DMPU as cosolvent)

To a solution of diisopropylamine (223 mg, 0.309 ml, 2.20 mmol) in THF (1 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 1.31 ml, 2.10 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and then cooled to -78°. DMPU (0.8 ml) was added dropwise ensuring efficient magnetic stirring during the addition. To the resulting colourless suspension at -78°C was added a solution of **(4)** (229 mg, 1.00 mmol) in THF (4 ml) dropwise, to give a yellow suspension. The cooling bath was removed for 3-5 min to allow complete dissolution of the suspension. The cooling bath was then replaced and the resulting deep yellow solution was stirred at -78°C for 1h. After this time the neat electrophile (1.00 mmol) was added dropwise and the mixture was stirred at -78°C for 20 min, then allowed to warm to 0°C over 30 min. 2M aqueous hydrochloric acid (3 ml) was added at 0°C and the mixture was stirred vigorously for 5 min then poured onto water (20 ml) and extracted with ether (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (9:1 - 3:1 v/v) as eluant afforded the adduct **(74)**.

i) Diethyl 5-Methyl-4-oxo-1,3-pyrrolidinedicarboxylate **(74a)**

Isolated as a colourless oil (178 mg, 73%, General Procedure B); δ_H 1.21-1.50 (9H, m, $C\underline{H}_3H_2$ x 2 and $CHC\underline{H}_3$) 3.52-4.66 (7.6H, m), 10.11 (0.4H, s(br), enol OH).

ii) Diethyl 4-Oxo-5-pentyl-1,3-pyrrolidinedicarboxylate **(74b)**

Isolated as a colourless oil (168 mg, 56%, General Procedure B); δ_H 0.82-0.95 (3H, m, $CH_2CH_2C\underline{H}_3$), 1.15-1.39 (11H, m), 1.45-2.38 (3H, m), 3.40-4.70 (7.6H, m), 10.10 (0.4H, s(br), enol OH).

iii) Diethyl 5-Benzyl-4-oxo-1,3-pyrrolidinedicarboxylate **(74c)**

Isolated as a colourless oil (163 mg, 51%, General Procedure A); δ_H 1.12-1.64 (6H, m, $C\underline{H}_3CH_2$ x 2), 2.70-3.52 (3.5H, m), 3.90-4.41 (4.6H, m), 4.53-5.10 (1.5H, m), 7.0-7.32 (5H, m, Ph), 10.10 (0.4H, s(br), enol OH).

iv) Diethyl 4-Oxo-5-(2-propenyl)-1,3-pyrrolidinedicarboxylate **(74d)**

Isolated as a colourless oil (151 mg, 56%, General Procedure B). This material was subjected to immediate deethoxycarbonylation according to the General Procedure A (see below).

v) Diethyl 3-Oxo-2-[3-(phenylmethoxy)propyl]-1-pyrrolidinedicarboxylate **(74e)**

Isolated as a colourless oil (268 mg, 71%); δ_H 1.22-1.35 (6H, m, $C\underline{H}_3CH_2$ x 2), 1.43-2.22 (4H, m $(C\underline{H}_2)_2$ CH_2O), 3.40-3.95 (3H, m), 4.05-4.75 (8.5H, m), 7.20-7.42 (5H, m, Ph), 10.11 (0.5H, s(br), enol OH).

vi) Diethyl 5-(1-Hydroxy-2-methylpropyl)-4-oxo-1,3-pyrrolidinedicarboxylate (74f)

Isolated as a colourless oil (265 mg, 88%); δ_H 0.88-1.06 (6H, m, CH$\underline{Me_2}$), 1.20-1.36 (6H, m, C$\underline{H_3}$CH$_2$ x 2), 1.79-2.22 (1H, m, C$\underline{H}$Me$_2$), 3.40-4.95 (8.8H, m), 10.22 (0.2H, s(br), enol OH) (alkyl OH not observed).

vii) Diethyl 5-(1-Hydroxyhexyl)-4-oxo-1,3-pyrrolidinedicarboxylate **(74g)**

Isolated as a colourless oil (234 mg, 71%). This material was subjected to immediate deethoxycarbonylation according to the General Procedure **B** (see below).

The adducts **(74a-g)** were not characterized by elemental analysis or high resolution mass determination, but were converted to the corresponding 2-substituted-3-pyrrolidinones **(75a-g)** (see below) for which analytical data were obtained.

(viii) Diethyl 5-[α-Hydroxy(phenylmethyl)]-4-oxo-1,3-pyrrolidinedicarboxylate **(74h)**

Isolated as a colourless oil (292 mg 87%); δ_H 1.16-1.36 (6H, m, C$\underline{H_3}$CH$_2$ x 2), 2.90 - 6.20 (9.7H, m), 7.16-7.40 (5H, m, Ph), 10.17 (0.3H, s(br), enol OH).

Deethoxycarbonylation of the Adducts (**74a-h**)

General Procedure A (aqueous oxalic acid/p-dioxane)

To a solution of adduct (**74**) (1.00 mmol) in p-dioxane (6 ml) was added 1M aqueous oxalic acid (4 ml) and the mixture was stirred at reflux for 16-48h. After cooling, the mixture was concentrated by evaporation under reduced pressure until the oxalic acid began to crystallize (approx. half x original volume). This residue was poured onto saturated aqueous sodium hydrogen carbonate solution (20 ml) and extracted with dichloromethane (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (5:1 - 2:1 v/v) as eluant afforded the 2-substituted-3-pyrrolidinone (**75**).

General Procedure B (NaCl/DMSO/aq)

To a solution of adduct (**74**) (1.00 mmol) in DMSO (3 ml) was added NaCl (64 mg, 1.10 mmol) and water (0.2 ml) and the mixture was stirred at 130-135°C for 2h. After cooling the mixture was poured onto saturated aqueous sodium chloride solution (30 ml) and extracted with dichloromethane (6 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (5:1 - 2:1 v/v) as eluant afforded the 2-substituted-3-pyrrolidinone (**75**).

i) Ethyl 2-Methyl-3-oxo-1-pyrrolidinecaboxylate (**75a**)

Isolated as a colourless oil (139 mg, 81%, General Procedure A) (Found: M^+, 171.0907. $C_8H_{13}NO_3$ requires 171.0894); ν_{max} (film) 1750, 1680 cm^{-1}; δ_H 1.29 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 1.34 (3H, d, J 7Hz, $CHC\underline{H}_3$), 2.48-2.72 (2H, m, 4-H_2), 3.62 (1H, m, 2-H), 3.88-4.04 (2H, m, 5-H_2), 4.12-4.27 (2H, m, $CH_3C\underline{H}_2$); δ_C

14.6 (CH_3), 16.3 (CH_3), 35.6 (C-4), 41.0 (C-5), 57.7 (C-2), 61.3 ($CH_3\underline{C}H_2$), 213.3 (C-3) (O-C=O not observed); m/z (70 eV E.I.) 171 (M^+, 15%), 143 (100), 126 (19), 114 (20).

ii) Ethyl 3-Oxo-2-pentyl-1-pyrrolidinecaboxylate (75b)

Isolated as a colourless oil (175 mg, 77%, General Procedure A) (Found : M^+, 227.1534. $C_{12}H_{21}NO_3$ requires 227.1519); υ_{max} (film) 1750, 1680 cm^{-1}; δ_H 0.87 (3H, t, J 7Hz, $CH_2CH_2C\underline{H}_3$), 1.10-1.42 (9H, m, $(C\underline{H}_2)_3CH_3$ and $C\underline{H}_3CH_2O$), 1.60-1.98 (2H, m(br), $CHC\underline{H}_2$), 2.43-2.70 (2H, m, 4-H_2), 3.59 (1H, m, 2-H), 3.90-4.10 (2H, m(br), 5-H_2), 4.10-4.30 (2H, m, $CH_3C\underline{H}_2O$); δ_C 13.8 (CH_3), 14.5 (CH_3), 22.3 (CH_2), 24.0 (CH_2), 31.4 (CH_2), 31.5 (CH_2), 36.1 (CH_2), 41.8 (CH_2), 61.4 (CH_2), 61.8 (C-2)(O-C=O and C-3 not observed); m/z (70eV E.I.) 227 (M^+, 7%), 199 (47), 156 (100), 115 (44).

iii) Ethyl 3-Oxo-2-phenylmethyl-1-pyrrolidinecarboylate (75c)

Isolated as a colourless oil (218 mg, 88%, General Procedure A) (Found: M^+, 247.1190. $C_{14}H_{17}NO_3$requires 247.1207); υ_{max} (film) 1745, 1680 cm^{-1}; δ_H 1.33 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 1.82-2.01 (1H, m(br)), 2.40 (1H, m), 2.78 (1H, m), 3.10 (1H, dd, J 14.5, 3Hz), 3.16-3.55 (1H, m(br)), 3.57-3.90 (1H, m(br)), 4.17-4.35 (3H, m(br)), 7.02-7.30 (5H, m, Ph); δ_C 14.76 ($\underline{C}H_3CH_2$), 36.4 (CH_2), 41.9 (CH_2), 61.5 (CH_2), 63.2 (C-2), 65.3 (CH_2), 126.9 (Ph_{CH}), 127.5 ($Ph_{Cquatemary}$), 128.5 (Ph_{CH}), 129.8 (Ph_{CH}) (O-C=O and C-3 not observed); m.z (70eV E.I.) 247 (M^+, 21%), 156 (90), 112 (21), 91 (24), 84 (100).

iv) Ethyl 3-Oxo-2-(2-propenyl)-1-pyrrolidinecarboxylate **(75d)**

Isolated as a colourless oil (132mg, 67%, General Procedure **A**); υ_{max} (film) 1750, 1690 cm^{-1}; δ_H 1.30 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 2.37-2.92 (4H, m, $C\underline{H}_2CH$=CH_2 and 4-H_2), 3.57 (1H, m, 2-H), 3.82-4.10 (2H, m(br), 5-H_2), 4.11-4.32 (2H, m, $CH_3C\underline{H}_2$), 5.01-5.16 (2H, m, CH=$C\underline{H}_2$), 5.60-5.78 (1H, m, $C\underline{H}$=CH_2); m/z (70eV E.I.) 197 (M^+, 3%), 159 (92), 112 (16), 84 (100). (Low eV E.I.) 197 (M^+, 9%), 156 (100). The spectroscopic data for **(75d)** are in agreement with those reported previously.[178]

v) Ethyl 3-Oxo-2-[3-(phenylmethoxy)propyl]-1-pyrrolidinecarboxylate **(75e)**

Isolated as a colourless oil (272 mg, 89%, General Procedure **A**) (Found: M^+, 305.1614. $C_{17}H_{23}NO_4$ requires 305.1625); υ_{max} (film) 1750, 1690 cm^{-1}; δ 1.24 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 1.45-2.05 (4H, m, $CHC\underline{H}_2C\underline{H}_2$), 2.39-2.68 (2H, m, 4-$H_2$), 3.44 (2H, t, J 6.5Hz, $CH_2C\underline{H}_2O$), 3.57 (1H, m, 2-H), 3.92-4.09 (2H, m(br), 5-H_2), 4.18 (2H, m, $CH_3C\underline{H}_2$), 4.97 (2H, s, $PhC\underline{H}_2$), 7.24-7.36 (5H, m, Ph); δ_C 14.6 ($\underline{C}H_3CH_2$), 24.8 (CH_2), 27.9 (CH_2), 36.1 (CH_2), 41.7 (CH_2), 61.4 (CH_2), 61.5 (C-2), 69.8 (CH_2), 72.8 (CH_2), 127.5 (Ph_{CH} x 2), 128.3 (Ph_{CH}) (O-C=O and C-3 not observed); m/z (70eV E.I.) 305 (M^+, 5%), 214 (64), 196 (26), 156 (41), 91 (100).

vi) Ethyl 2-(1-Hydroxy-2-methylpropyl)-3-oxo-1-pyrrolidinecarboxylate **(75f)**

Isolated as a colourless oil (209 mg, 91%, General Procedure **B**). An analytical sample was obtained by bulb-to-bulb distillation, b.p. 180°C/0.1 mmHg (Found: C, 57.50; H, 8.51; N, 6.05%. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11%); υ_{max} (film) 3420 (br), 1750, 1670 cm^{-1}, δ_H 0.80-1.18 (6H, m, $CH\underline{Me}_2$), 1.23-1.38 (3H, m, $C\underline{H}_3CH_2$), 1.65-2.66 (4H, m), 3.06-4.32 (6H, m); δ_C 14.6

(CH_3), 19.3 (CH_3), 30.4 and 30.8 (<u>C</u>HMe$_2$), 36.7 and 36.9 (C-4), 42.4 and 43.6 (C-5), 61.7 and 61.9 (CH_3<u>C</u>H_2), 64.0 and 65.5 (C-2), 78.7 and 80.1 (<u>C</u>HOH) (O-C=O and C-3 not observed); m/z (C.I.) 230 (MH^+, 49%), 212 (26), 198 (5), 186 (4), 170 (2), 158 (28), 157 (100), 156 (36).

vii) <u>Ethyl 2-(1-Hydroxyhexyl)-3-oxo-1-pyrrolidinecarboxylate (75g)</u>

Isolated as a colourless oil (198 mg, 77%, General Procedure **B**). An analytical sample was obtained by bulb-to-bulb distillation, b.p. 200°C/0.04 mmHg (Found: C, 60.60; H, 9.10; N, 5.45%. $C_{13}H_{23}NO_4$ requires C, 60.68; N, 9.01; N, 5.44%); υ_{max} (film) 3420 (br), 1750, 1670 cm^{-1}; δ_H 0.80-0.96 (3H, m, CH_2CH_2<u>C</u>H_3), 1.16-1.75 (11H, m, ($C\underline{H}_2)_4CH_3$ and $C\underline{H}_3CH_2O$), 2.42-2.70 (2H, m, 4-H_2), 3.60-4.31 (6H, m) (OH not observed); δ_C 13.9 (CH_3), 14.6 (CH_3), 22.5 (CH_2), 25.5 (CH_2), 31.6 (CH_2), 32.8 (CH_2), 34.1 (CH_2), 36.6 (CH_2), 42.4 and 43.2 (C-5), 61.8 and 62.0 ($CH_3\underline{C}H_2O$), 65.6 and 67.5 (C-2), 73.5 and 73.9 (<u>C</u>HOH) (O-C=O and C-3 not observed); m/z (C.I.) 258 (MH^+, 12%), 240 (16), 212 (1), 198 (3), 158 (49), 157 (100).

viii) <u>Ethyl 2-[α-Hydroxy(phenylmethyl)]-3-oxo-1-pyrrolidinecarboxylate (75h)</u>

Obtained as a 3:2 mixture of diastereoisomers in a mixture with **(5)** (colourless oil, 116 mg, 3:1 **(75h)**:**(5)** (^1H nmr), 37% of **(75h)**, General Procedure A); υ_{max} (film) 3360 (br), 1750, 1670 cm^{-1}; δ_H 1.23-1.40 (3H, m, $C\underline{H}_3CH_2$ **(75h)** and (5)), 1.85-2.18 (1H, m(br), 4-H_A **(75h)** major diastereoisomer), 2.26-2.55 (2H, m(br), 4-H_2 **(75h)** minor diastereoisomer), 2.62 (2H, t, J 7.5Hz, 4-H_2 **(5)**), 2.66-2.84 (1H, m(br), 4-H_B **(75h)** major diastereoisomer)), 3.59-4.06 (1H, m(br), 2-H, **(75h)** both diastereoisomers), 3.80 (2H, s, 2-H_2 **(5)**), 3.83 (2H, t, J 7.5Hz, 5-H_2 **(5)**), 4.08-4.39 (2H, m, $CH_3C\underline{H}_2$ **(75h)** and **(5)**), 4.55 (1H, s, C<u>H</u>OH, **(75h)** minor diastereoisomer), 5.23 (1H, m, C<u>H</u>OH, **(75h)** major diastereoisomer), 5.77 (1H, m(br), OH **(75h)** both diastereoisomers), 7.16-7.40 (5H, m, Ph **(75h)** both diastereoisomers); m/z (C.I.) 264 (MH^+, 2%, **(75h)**), 262 (1), 240 (20), 230 (7), 158 (100), 157 (44), 128 (19), 107 (61).

Diethyl 5,5-Dipentyl-4-oxo-1,3-pyrrolidinedicarboxylate **(76)**

General Procedure **A** for reaction of the dianion **(72)** with electrophiles was followed using 2.69 equivalents of *n*-butyllithium (1.6M in hexane, 1.68 ml, 2.69 mmol) instead of 2.10 equivalents. Alkylation with 1-bromopentane (151mg, 0.124 ml, 1 mmol) and work-up according to the general procedure gave an oil which was chromatographed on silica gel using petrol-ethyl acetate (4:1 v/v) as eluant to give first eluted **(76)** (121 mg, 33%) as a colourless oil; δ_H 0.76-0.98 (6H, m, $CH_2CH_2C\underline{H}_3$ x 2), 0.99-2.38 (22H, m, $(C\underline{H}_2)_4CH_3$ x 2 and $C\underline{H}_3CH_2O$ x 2), 3.47 (O.4H, m), 3.93 (0.4H, m), 4.02-4.34 (5.6H, m), 10.10 (0.6H, s(br), enol OH). This material was converted to the 2,2-dipentyl-3-pyrrolidinone **(77)** without further characterization.

Further elution gave **(74b)** (108 mg, 36%) as a colourless oil.

Ethyl 2,2-Dipentyl-3-oxo-1-pyrrolidinecarboxylate **(77)**

Dipentyl adduct **(76)** (93 mg, 0.252 mmols) was subjected to deethoxycarbonylation according to General Procedure **B** (DMSO (1 ml), H_2O (0.2 ml), NaCl (15 mg)) to give, after chromatography using petrol-ethyl acetate (4:1 v/v) as eluant, **(77)** (65 mg, 88%) as a colourless oil. An analytical sample was obtained by bulb-to-bulb distillation, b.p. 180°C/0.05 mmHg (Found: C, 69.10; H, 10.80; N, 4.70%. $C_{17}H_{31}NO_3$ requires C, 68.65; H, 10.50; N, 4.71%); υ_{max} (film) 1785, 1705 cm^{-1}; δ_H 0.84 (6H, t, J 7Hz, $CH_2CH_2C\underline{H}_3$ x 2), 1.04-1.36 (15H, m), 1.54-1.75 (2H, m), 1.97 (1H, m), 2.20 (1H, m), 2.48 (2H, m, 4-H_2), 3.72 (2H, q, J 8Hz, 5-H_2), 4.21 (2H, m, $CH_3C\underline{H}_2O$); δ_C 13.8 (CH_3), 14.6 (CH_3), 14.7 (CH_3), 22.2 (CH_2), 22.4 (CH_2), 23.9 (CH_2), 24.1 (CH_2), 31.7

(CH_2), 35.6 (CH_2), 36.1 (CH_2), 37.3 (CH_2), 42.1 (CH_2), 42.4 (CH_2), 60.7 and 61.1 ($CH_3\underline{C}H_2O$), 70.6 and 70.8 (C-2), 154.0 (O-C=O), 217.0 (C-3); m/z (C.I.) 298 (MH^+, 38%), 280 (3), 269 (6), 252 (3), 240 (3), 226 (100).

Ethyl 2-Methyl-3-oxo-2-pentyl-1-pyrrolidinecarboxylate **(80)**

To a stirred solution of diisopropylamine (174 mg, 0.241 ml, 1.72 mmol) in THF (1 ml) at -78°C was added *n*-butyllithium (1.6M in hexane, 1.03 ml, 1.64 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and then cooled to -78°C. DMPU (0.6 ml) was added dropwise ensuring efficient stirring during the addition. To the resulting colourless suspension at -78°C was added a solution of **(4)** (179 mg, 0.781 mmol) in THF (4 ml) dropwise, to give a yellow suspension. The cooling bath was removed for 3-5 min to allow complete dissolution of the suspension. The cooling bath was then replaced and the resulting deep yellow solution was stirred at -78°C for 1h. After this time iodomethane (111 mg, 49 µl, 0.782 mmol) was added and the reaction mixture was allowed to warm to 0°C over 20 min. A solution of LDA (1M, 0.78 ml, 0.78 mmol) (prepared by adding *n*-butyllithium (1.6M in hexane, 3.13 ml, 5.00 mmol) to a solution of diisopropylamine (506 mg, 0.70 ml, 5.00 mmol) in THF (1.10 ml) dropwise at 0°C), was then added dropwise and the mixture was stirred at 0°C for 20 min. The resulting deep red solution was treated with 1-bromopentane (130 mg, 0.107 ml, 0.860 mmol) and the mixture was stirred at 0°C for a further 20 min. 2M aqueous hydrochloric acid (2 ml) was added at 0°C and the mixture was stirred vigorously for 5 min then poured onto water (20 ml) and extracted with ether (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl aceate (4:1 v/v) as eluant gave **(79)** (148 mg, 60%) as a colourless oil which was subjected to deethoxycarbonylation according to General Procedure **B** (DMSO (2 ml), H_2O (0.2 ml), NaCl (28 mg)) to give, after chromatography using petrol-ethyl acetate (4:1 v/v), **(80)** (95 mg, 83%) (50% overall from **(4)**) as a colourless oil.

An analytical sample was obtained by bulb-to-bulb distillation, b.p. 160°C/0.01 mmHg (Found : C, 64.80; H, 9.75; N, 5.90%. $C_{13}H_{23}NO_3$ requires C, 64.70; H, 9.61; N, 5.80%); υ_{max} (film) 1755, 1690 cm^{-1}; δ_H 0.84 (3H, t, J 7Hz, $CH_2CH_2C\underline{H}_3$), 1.10-1.43 (12H, m), 1.62-1.78 (1H, m(br)), 2.04 (0.5H, m), 2.25 (0.5H, m), 2.38-2.70 (2H, m, 4-H_2), 3.60-3.82 (2H, m(br), 5-H_2), 4.12-4.34 (2H, m, $CH_3C\underline{H}_2O$); δ_C 13.8 (CH_3), 14.5 (CH_3), 22.0 and 23.3 (CH_3), 22.2 (CH_2), 24.2 (CH_2), 31.7 (CH_2), 34.5 (CH_2), 35.9 (CH_2), 37.1 (CH_2), 41.2 (CH_2), 60.7 and 61.1 ($CH_2\underline{C}H_2O$), 66.6 (C-2), 216.0 (C-3); m/z (Low eV E.I.) 241 (M^+, 9%), 213 (60), 170 (100), 157 (64), 42 (20), 29 (12).

1,4-Dioxa-7-azaspiro[4.4]nonane-6-propanol **(83)**

To a solution of **(75e)** (375 mg, 1.23 mmol) and toluene-p-sulphonic acid (10 mg) in benzene (50 ml) was added ethane-1,2-diol (144 mg, 0.13 ml, 2.32 mmol) and the mixture was heated at reflux under azeotropic conditions (Dean-Stark) for 16h. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (30 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (10 ml). The organic layer was collected and the aqueous layer was extracted with a further portion of dichloromethane (5 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (4:1 v/v) as eluant gave **(81)** (344 mg, 80%) as a colourless oil; δ_H 1.24 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 1.39-1.60 (1H, m), 1.62-1.84 (3H, m), 1.87-1.99 (1H, m), 2.01-2.25 (1H, m), 3.35-3.55 (4H, m), 3.56-3.75 (1H m), 3.86-4.03 (4H, m, OCH_2CH_2O), 4.05-4.23 (2H, m, $CH_3C\underline{H}_2$), 4.50 (2H, s, $C\underline{H}_2Ph$), 7.28-7.38 (5H, m, Ph). To a solution of **(81)** (328 mg, 0.939 mmol) in diethylene glycol (4 ml) were added KOH pellets (300mg, 5.35 mmol) and the mixture was stirred at 140°C for 16h and then at 160°C for 4 hrs. The mixture was cooled, poured onto saturated aqueous ammonium chloride solution (30 ml) and extracted with chloroform (6 x 10 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude amine **(82)** as a brown oil which was dissolved in methanol (8 ml) and subjected to atmospheric hydrogenation in the presence of 10% Pd/C catalyst (20 mg) for 48h. After this time, the catalyst was removed by filtration through celite and the filtrate was evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using ethyl acetate-methanol-triethylamine (8:1:1 v/v/v) afforded **(83)** (135 mg, 77% for two steps) as a straw-coloured oil (Found : M^+, 187.1213. $C_9H_{17}NO_3$ requires 187.1208); υ_{max} (film) 3300 (br); δ_H 1.22-1.44 (1H, m), 1.48-1.71 (1H, m), 1.73-1.90 (2H, m), 1.96 (2H, t, J 7.5 Hz), 2.69-2.94 (2H, m(br), NH and OH) 2.77 (1H, dd, J 11, 2.5 Hz), 2.90-3.11 (2H, m), 3.57 (1H, m), 3.62-3.76 (1H, m), 3.85-4.03 (4H, m, OCH_2CH_2O); m/z (70 eV E.I.) 187 (M^+, 2%), 156 (4), 115 (8), 101 (10), 87 (30), 45 (100). (C.I.) 188 (MH^+, 100%), 170 (14), 156 (6), 126 (9), 107 (30).

Pyrrolizidine **(84)** -- Picrate salt

To a solution of **(83)** (100 mg, 0.534 mmol) in THF (5 ml) was added diisopropylethylamine (137 mg, 0.19 ml, 1.06 mmol), triphenylphosphine (279 mg, 1.06 mmol) and carbon tetrabromide (352 mg, 1.06 mmol) and the mixture was stirred at room temperature for 1h. The solvent was removed by evaporation under reduced pressure and the residue was partitioned between saturated aqueous sodium hydrogen carbonate solution (10 ml) and dichloromethane (10 ml). The organic phase was collected and the aqueous phase was extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried (K_2CO_3) and evaporated under reduced pressure to give **(84)** (24 mg, 27%) as a tan oil which was dissolved in methanolic HCl (2 ml) and evaporated under reduced pressure. The residue was dissolved in water (2 ml) and the solution was treated with a saturated aqueous solution of picric acid (5 ml). The resulting suspension was allowed to stand at room temperature for 48h. After this time, the yellow granular crystals which had formed were collected by filtration, affording **(85)** (7.5 mg, 13.3%), m.p. 204-206°C (dec.) (Found : C, 45.10; H, 4.49; N, 14.00%. $C_{15}H_{18}N_4O_9$ requires C, 45.23; H, 4.55; N, 14.07%); υ_{max} ($CHCl_3$) 1605, 1315 cm^{-1}; δ_H 2.05-2.24 (5H, m, 6-H_2, 7-H_2 and 2-H_A), 2.31-2.45 (1H, m, 2H_B), 2.98-3.13 (2H, m, 3-H_A and 5-H_A), 3.65-3.79 (1H, m, 5-H_B), 3.94-4.10 (5H, m, OCH_2CH_2O and 3-H_B), 4.21-4.32 (1H, m, 7a-H); m/z (+FAB) 170 (M^+, 100%). (-FAB) 228 (M^-, 4%) 183 (100).

Aldol-Type Reaction of Dianion (72) with Aldehyde (26) -- **Medium Scale Preparation of Adduct (86)**

To a solution of diisopropylamine (2.23 g, 3.09 ml, 22.0 mmol) in THF (20 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 13.13 ml, 21.0 mmol) dropwise. The resulting solution was stirred at 0°C for 10 min and then cooled to -78°C. DMPU (5 ml) was then added dropwise, ensuring efficient magnetic stirring during the addition. To the resulting colourless suspension at -78°C was added a solution of **(4)** (2.29 g, 10.0 mmol) in THF (30 ml) dropwise, to give a yellow suspension. The reaction mixture was allowed to warm to -60°C and stirred at that temperature for 10-15 min to allow complete dissolution of the suspension. The resulting deep yellow solution was recooled to -78°C and stirred for 1h. After this time a solution of **(26)** (2.51 g, 10.0 mmol) in THF (10 ml) was added dropwise at -78°C and the mixture was stirred at -78°C for 20 min, then allowed to warm to 0°C over 20 min and stirred at 0°C for a further 20 min. 2M Aqueous hydrochloric acid (25 ml) was then added at 0°C and the mixture was stirred vigorously for 5 min then poured onto water (150 ml) and extracted with ether (4 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed on silica gel using petrol-ethyl acetate (70:30 v/v) as eluant to give the adduct **(86)** (3.20 g, 67% (uncorrected for contamination by **(88)**) as a straw-coloured oil (mixture of isomers) which was used without further purification.

<u>8-*O*-benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-6,7-*O*-isopropylidene--oct-3-ulose **(87b)** and</u>

<u>8-*O*-benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-6,7-*O*-isopropylidene-L-*galacto*-oct-3-ulose **(87d)**</u>

The adduct **(86)** (2.88 g, 6.00 mmol) was dissolved in DMSO (20 ml) and water (2 ml) followed by NaCl (0.37 g, 6.33 mmol) were added. The mixture was heated at 130-135°C for 2h, cooled, poured onto saturated aqueous sodium chloride solution (150 ml) and extracted with dichloromethane (6 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Repeated column chromatography of the residue on silica gel using petrol-ethyl acetate (3:1 - 3:2 v/v) as eluant afforded, in order of elution:

(i) **(87b)** + 20 mol% **(88)** + trace **(87a)** (see Appendix 1, HPLC trace 2) (664 mg, equivalent to 575 mg of **(87b)**, 14.1% from **(4)**) as a straw-coloured oil. A purified sample of **(87b)** was obtained by semi-preparative HPLC (see Appendix 1) as a colourless oil (Found : MH^+, 408.2022. $C_{21}H_{30}NO_7$ requires 408.2014); υ_{max} (film) 3380 (br), 1755, 1690 cm^{-1}; δ_H (400 MHz) 1.22-1.35 (6H, m, $\underline{CH_3}CH_2$ and $OCMe_A$), 1.37 (3H, s, $OCMe_B$), 2.45-2.65 (2H, m, 2-H_2), 3.52-3.80 (4H, m(br)), 3.81-3.95 (1H, m(br)), 4.10 (1H, t, J 9 Hz), 4.13-4.28 (4H, m), 4.57 (1H, d, J 13 Hz, $PhC\underline{H_A}$), 4.62 (1H, d, J 13 Hz, $PhC\underline{H_B}$), 5.13-5.26 (1H, m(br), OH), 7.29-7.37 (5H, m, Ph); δ_C 14.6 ($\underline{C}H_3CH_2$), 26.2 ($OC\underline{Me_A}$), 26.9 ($OC\underline{Me_B}$), 35.6 (C-2), 42.5 (C-1), 62.5 (CH_2), 67.2 (CH), 70.7 (CH_2), 73.4 (CH_2), 76.1 (CH), 76.5 (CH), 80.3 (CH), 109.9 ($O\underline{C}Me_2$), 127.6 (Ph_{CH}), 128.3 (Ph_{CH}), 138.0 ($Ph_{Cquaternary}$), 157.3 (O-C=O), 207.8 (C-3); m/z (C.I.) 408 (MH^+, 84%), 392 (17), 364 (17), 350 (59), 332 (13), 318 (11), 300 (17), 282 (6), 268 (7), 157 (63), 91 (100).

(ii) Mixed fractions (652 mg, approx. 15% **(87a/b/c/d)** from **(4)**) as a straw-coloured oil;

(iii) **(87d)** + trace **(87c)** (see Appendix 1, HPLC trace 3) (477 mg, 11.7% from **(4)**) as a straw-coloured oil. A purified sample of **(87d)** was obtained by semi-preparative HPLC (see Appendix 1) as a colourless oil (Found : MH^+, 408.2022. $C_{21}H_{30}NO_7$ requires 408.2014); υ_{max} (film) 3400 (br), 1755, 1685 cm^{-1}; δ_H (400 MHz) 1.28 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 1.36-1.38 (6H, 2 x s, $OC\underline{Me}_2$), 2.43-2.53 (2H, m, 2-H_2), 3.48 (1H, t, J 8.5 Hz), 3.57-3.71 (2H, m), 3.72-3.86 (2H, m), 3.95-4.08 (2H, m), 4.10-4.27 (4H, m), 4.58 (2H, s, $PhC\underline{H}_2$), 7.23-7.49 (5H, m, Ph); δ_C 15.0 ($\underline{C}H_3CH_2$), 27.0 ($OC\underline{Me}_A$), 27.2 ($OC\underline{Me}_B$), 37.1 (C-2), 43.9 (C-1), 6.20 (CH_2), 64.5 (CH), 70.8 (CH_2), 74.1 (CH_2), 76.0 (CH), 78.9 (CH), 79.8 (CH), 110.0 ($O\underline{C}Me_2$), 128.3 (Ph_{CH}), 128.5 (Ph_{CH}), 129.0 (Ph_{CH}), 128.5 (Ph_{CH}), 129.0 (Ph_{CH}), 137.2 ($Ph_{Cquaternary}$), 156.2 (O-C=O) (C-3 not observed); m/z (C.I.) 408 (MH^+, 13%), 350 (14), 332 (3), 318 (4), 298 (9), 242 (10), 157 (82), 107 (44), 91 (100).

Purified samples of the minor diastereoisomers **(87a)** and **(87c)** were also obtained by semi-preparative HPLC (see Appendix 1) as colourless oils:

(87a) + 10 mol% **(87c)**; δ_H (400 MHz, 60°C) 1.21 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$, major isomer), 1.28 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$, minor isomer), 1.35 (6H, s, $OC\underline{Me}_2$, major isomer), 1.37-1.40 (6H, 2 x s, $OC\underline{Me}_2$ minor isomer), 2.43-2.66 (2H, m, 2-H_2), 3.34 (1H, d, J 13 Hz, major isomer), 3.52-3.60 (1H, m, major isomer), 3.55-3.66 (2H, m), 3.70 (2H, m, minor isomer), 3.83-4.28 (6H, m), 4.29-4.37 (1H, m, major isomer), 4.50-4.58 (2H,m, $PhC\underline{H}_2$), 7.21-7.36 (5H, m, Ph); m/z (CI.) 408 (MH^+, 6%), 332 (1), 268 (100), 251 (48), 210 (29), 175 (72), 158 (82), 129 (8), 108 (29), 91 (15).

(87c); δ_H (400 MHz, 60°C) 1.28 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 1.37-1.40 (6H, 2 x s, $OC\underline{Me}_2$), 2.45-2.59 (2H, m, 2-H_2), 3.55-3.66 (2H, m), 3.70 (2H, m), 3.83-4.30 (7H, m), 4.51-4.60 (2H, m, $PhC\underline{H}_2$), 7.20-7.36 (5H, m, Ph); m/z (C.I.) 408 (MH^+, 100%), 268 (94), 251 (43), 210 (15), 175 (51), 158 (45), 108 (24), 91 (14).

(For additional variable temperature ^1H nmr spectra of **(87a)** and **(87c)**, see Appendix 2).

8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-6,7-*O*-isopropylidene-L-*glycero*-D-*gluco*-octitol **(90)**

To a solution of diisobutylaluminium hydride (1.5M in toluene, 1.7 ml, 2.55 mmol) in THF (3 ml) at -78°C was added a solution of **(87d)** (407 mg, 1.00 mmol) in THF (2 ml) dropwise. The reaction mixture was stirred at -78°C for 15 min and then saturated aqueous ammonium chloride solution (2 ml) was added dropwise at -78°C. The mixture was allowed to warm to room temperature over 30 mins, then poured onto 2M aqueous hydrochloric acid (20 ml) and extracted with ethyl acetate (5 x 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (1:4 v/v) as eluant afforded **(90)** (328 mg, 80%) as a colourless oil which crystallised upon storage at -20°C. An analytical sample was obtained by recrystallization from ether (-20°C) affording colourles needles, m.p. 93-94°C (Found : C, 61.70; H, 7.71; N, 3.39%. $C_{21}H_{31}NO_7$ requires C 61.60; H, 7.63; N, 3.42%); υ_{max}(film) 3400 (br), 1660 cm^{-1}; δ_H 1.28 (3H, t, J 7Hz, $C\underline{H}_3CH_2$), 1.44 (3H, s, $OCMe_A$), 1.46 (3H, s, $OCMe_B$), 1.60-2.01 (2H, m(br), 2-H_2), 3.42-3.99 (7H, m), 4.00-4.23 (3H, m), 4.25-4.43 (1H, m,(br)), 4.44-4.55 (1H, m(br)), 4.57-4.67 (2H, m, $PhC\underline{H}_2$), 6.33 (1H, s(br), OH), 7.22-7.40 (5H, m, Ph); δ_C 14.5 ($\underline{C}H_3CH_2$), 26.5 ($OC\underline{Me}_A$), 26.9 ($OC\underline{Me}_B$), 32.2 (C-2), 46.1 (C-1), 62.1 (CH_2), 69.2 (CH), 71.1 (CH_2), 71.4 (CH), 73.4 (CH_2), 73.7 (CH), 77.4

(CH), 80.6 (CH), 109.9 (O$\underline{C}$Me$_2$), 127.4 (Ph$_{CH}$), 127.6 (Ph$_{CH}$), 128.2 (Ph$_{CH}$), 138.2 (Ph$_{Cquaternary}$) (O-C=O not observed); m/z (C.I.) 410 (MH$^+$, 19%), 394 (3), 364 (13), 352 (8), 226 (7), 188 (38), 158 (72), 141 (39), 91 (100).

8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-6,7-*O*-isopropylidene-octitol **(91)**

To a solution of diisobutylaluminium hydride (1.5M in toluene, 1.7 ml, 2.55 mmol) in THF (3 ml) at -78°C was added a solution of **(87b)** (407 mg, 1.00 mmol (0.87 mmol corrected for contamination by **(88)**) in THF (2 ml) dropwise. The reaction mixture was stirred at -78°C for 3h and a further portion of diisobutylaluminium hydride (1.5M in toluene, 0.5 ml, 0.75 mmol) was added dropwise. After stirring at -78°C for a further 1h, the reaction mixture was quenched at -78°C with saturated aqueous ammonium chloride solution (2 ml). The mixture was allowed to warm to room temperature over 30 min then poured onto 2M aqueous hydrochloric acid (20 ml) and extracted with ethyl acetate (5 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (60:40 - 30:70 v/v) as eluant afforded **(91)** (280 mg, 68% (77% based on **(87b)**) as a colourless oil (Found : MH$^+$, 410.2179. $C_{21}H_{32}NO_7$ requires 410.2170); υ_{max} (film) 3400 (br), 1680 cm^{-1}; δ_H 1.26 (3H, t, J 7 Hz, C$\underline{H_3}$CH$_2$), 1.43 (6H, s, OC$\underline{Me_2}$), 1.92-2.03 (2H, m, 2-H$_2$), 3.40-4.42 (11H, m), 4.43-4.65 (4H, m), 7.22-7.41 (5H, m, Ph); δ_C 14.6 ($\underline{C}$H$_3$CH$_2$), 26.7 (OCMe$_A$), 26.9 (OCMe$_B$), 33.5 (C-2), 44.6 and 44.8 (C-1), 61.7 (CH$_2$), 64.7 (CH), 68.9 (CH), 70.7 (CH$_2$), 72.1 and 72.5 (CH), 73.1 (CH), 73.5 and 73.7 (CH$_2$), 80.5 (CH), 109.8 (O$\underline{C}$Me$_2$), 127.6 (Ph$_{CH}$), 127.8 (Ph$_{CH}$), 127.9 (Ph$_{CH}$), 128.4 (Ph$_{CH}$) (Ph$_{Cquaternary}$ and O-C=O not observed); m/z (C.I.) 410 (MH$^+$, 72%), 394 (10), 352 (44), 226 (15), 188 (41), 158 (100), 141 (60), 91 (97).

<u>Large Scale Preparation of Adduct (86) and Octuloses (87b) and (87d)</u>

To a solution of diisopropylamine (11.13 g, 15.42 ml, 110 mmol) in THF (100 ml) at 0°C was added *n*-butyllithium (1.6M in hexane, 65.6 ml, 105 mmol) dropwise over 30 min. The resulting solution was stirred at 0°C for 10 min and then cooled to -78°C. DMPU (25 ml) was added dropwise ensuring efficient magnetic stirring during the addition. To the resulting colourless suspension was added a solution of **(4)** (11.45 g, 50 mmol) in THF (150 ml) dropwise over 30 min. The reaction mixture was allowed to warm to -60°C and stirred at that temperature until complete dissolution of suspended solids had occurred. The resulting deep yellow solution was then recooled to -78°C and stirred for 1hr. After this time a solution of aldehyde **(26)** (12.50 g, 50 mmol) in THF (50 ml) was added dropwise over 20 min and the mixture was stirred at -78°C for 20 min, then allowed to warm to 0°C over 30 min and stirred at 0°C for a further 20 min. 2M Aqueous hydrochloric acid (100 ml) was added dropwise at 0°C over 20 min and the mixture was poured onto water (600 ml) and extracted with ether (4 x 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (70:30 v/v) as eluant afforded the **(86)** (17.20 g, 72% (65% corrected for contamination by **(88)**) as a straw-coloured oil (mixture of isomers). This material was dissolved in DMSO (100 ml) and water (10 ml) followed by NaCl (2.93 g. 50.1 mmol) were added. The mixture was heated at 130-135°C for 2h, cooled, poured onto saturated aqueous ammonium chloride solution (600 ml) and extracted with ether (1 x 200 ml then 3 x 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude mixture of the octuloses **(87a-d)** and alcohol **(88)** (15.81 g) (**(87a)**:**(87b)**:**(87c)**:**(87d)** ratio 10:30:11:27 plus approx. 16 mol% **(88)** (see Appendix 1, HPLC trace 1)) as an orange oil. Repeated column chromatography of this mixture on silica gel using petrol-ethyl acetate (3:1 - 3:2 v/v) as eluant afforded, in order of elution:

(i) a 1:1 mixture (by ^{1}H nmr) of **(87b)** and **(88)** (4.33 g equivalent to 2.68 g **(87b)**, 13.2% from **(4)**) as a straw-coloured oil;

(ii) mixed fractions (4.41 g, approx. 21% from **(4)**) as a straw-coloured oil;

(iii) **(87d)** (2.30 g, 11.3% from **(4)**) as a straw-coloured oil.

8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-6,7-*O*-isopropylidene-L-*glycero*-D-*gluco*-octitol **(90)**

Octulose **(87d)** (2.22 g, 5.45 mmol) was reduced as described above to give, after chromatography **(90)** (1.42 g, 64%) as a colourless oil.

8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-6,7-*O*-isopropylidene-octitol **(91)**

The 1:1 mixture of **(87b)** and **(88)** obtained from the large scale preparation was reduced as follows. To a solution of diisobutylaluminium hydride (1.5M in toluene, 20 ml, 30 mmol) in THF (25 ml) at -78°C was added a solution of **(87b)**/**(88)** (4.30 g equivalent to 6.53 mmol **(87b)**) in THF (40 ml) dropwise over 20 min. The reaction mixture was stirred at -78°C for 1h, then saturated aqueous ammonium chloride solution (25 ml) was added dropwise at -78°C and the mixture was allowed to warm to room temperature over 30-40 min. The mixture was poured onto 2M aqueous hydrochloric acid (150 ml) and extracted with ethyl acetate (5 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (40:60 v/v) as eluant afforded **(95)** (1.44 g, 54%) as a colourless oil.

The Synthesis of 8-Epicastanospermine (100) from Octitol (90)

i) 8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-3,5;6,7-di-*O*-isopropylidene-L-*glycero*-D-*gluco*-octitol **(96)**

To a solution of **(90)** (1.41 g, 3.45 mmol) in chloroform (50 ml) was added 2,2-dimethoxypropane (0.54 g, 0.64 ml, 5.18 mmol) followed by toluene-p-sulphonic acid (10 mg). The mixture was boiled until 25 ml of solvent had evaporated and the resulting concentrated solution was diluted with chloroform (25 ml), treated with a further portion of 2,2-dimethoxypropane (0.64 ml, 5.18 mmol) and boiled until a further 25 ml of solvent had evaporated. The resulting concentrated solution was diluted once more with chloroform (25 ml), boiled until 20 ml of solvent had evaporated, cooled, diluted with dichloromethane (30 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (20 ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel using petrol-ethyl acetate (1:1 v/v) as eluant afforded **(96)** (1.19 g, 77%) as a colourless oil (Found : MH^+, 450.2492. $C_{24}H_{36}NO_7$ requires 450.2482); υ_{max} (film) 1685 cm^{-1}; δ_H 1.20 (3H, s, $OCMe_A$), 1.25 (3H, t, J 7 Hz, $C\underline{H}_3CH_2$), 1.41 (3H, s, $OCMe_B$), 1.43 (3H, s, $OCMe_C$), 1.45 (3H, s, $OCMe_D$), 1.62-1.89 (2H, m, 2-H_2), 3.40-3.56 (2H, m), 3.68 (1H, dd, J 11, 2 Hz), 3.81-3.92 (2H, m), 3.93-4.06 (2H, m), 4.07-4.18 (3H, m), 4.47-4.63 (1H, m), 4.53 (1H, d, J 12.5 Hz, $PhC\underline{H}_A$), 4.67 (1H, d, J 12.5 Hz, $PhC\underline{H}_B$), 7.20-7.41 (5H, m, Ph); m/z (C.I.) 450 (MH^+, 9%), 434 (9), 406 (7), 392 (16), 284 (9), 270 (10), 228 (12), 210 (4), 200 (4), 170 (7), 158 (7), 141 (100).

(ii) <u>1,2,4-Trideoxy-1,4,-imino-3,5;6,7-di-*O*-isopropylidene-L-*glycero*-D-*gluco*-octitol (98)</u>

A solution of **(96)** (1.18 g, 2.62 mmol) in methanol (5 ml) was added to propane-1,2-diol (20 ml) and the mixture was treated with KOH pellets (2.20 g, 39.2 mmol) and stirred at 140°C for 16h. After cooling, the reaction mixture was poured onto saturated aqueous ammonium chloride solution (140 ml) and extracted with ether (7 x 20ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure to give octitol **(97)** as a brown oil which was dissolved in methanol (60 ml) and subjected to atmospheric hydrogenation in the presence of 10% Pd/C (50 mg) for 48h. After this time, the catalyst was removed by filtration through celite and the filtrate was evaporated under reduced pressure to give a colourless crystalline solid. Recrystallization from ethyl acetate-petrol gave **(98)** (461 mg, 61%) as colourless prisms, m.p. 160-161°C, $[\alpha]^{19}_D$ -1.6° (c 1.59 in $CHCl_3$) (Found : C, 58.50; H, 9.00; N, 4.77%. $C_{14}H_{25}NO_5$ requires C, 58.52; H, 8.77; N, 4.87%); υ_{max} (nujol mull) 3100 (br); δ_H 1.39 (3H, s, $OCMe_A$), 1.40 (3H, s, $OCMe_B$), 1.42 (3H, s, $OCMe_C$), 1.49 (3H, s, $OCMe_D$), 1.75-2.03 (2H, m, 2-H_2), 2.87 (1H, t, J 2.4 Hz), 2.96 (1H, m), 3.24 (1H, dt, J 11, 8 Hz), 3.64-3.82 (2H, m), 3.94-4.06 (2H, m), 4.13 (1H, dd, J 7.5, 2.4 Hz), 4.38 (1H, m); δ_C 19.2 ($OC\underline{Me}_A$), 26.9 ($OC\underline{Me}_B$), 27.0 ($OC\underline{Me}_C$), 29.4 ($OC\underline{Me}_D$), 33.1 (C-2), 44.4 (C-1), 56.6 (CH), 63.4 (CH_2), 70.8 (CH), 72.0 (CH), 77.6 (CH), 81.0 (CH), 98.5 ($O\underline{C}Me_2$), 109.2 ($O\underline{C}Me_2$); m/z (C.I.) 288 (MH^+, 62%), 272 (11), 229 (9), 214 (7), 69 (100).

iii) **<u>8-Epicastanospermine (100) and 8-Epicastanospermine Hydrochloride (100a)</u>**

To a solution of **(98)** (287 mg, 1.00 mmol) in THF (6 ml) were added sequentially diisopropylethylamine (258 mg, 0.348 ml, 2.00 mmol), triphenylphosphine (524 mg, 2.00 mmol) and carbon tetrabromide (664 mg, 2.00 mmol) and the mixture was stirred at room temperature for 16h. After this time, the mixture was poured onto saturated aqueous sodium hydrogen carbonate solution (20 ml) and extracted with dichloromethane (4 x 10 ml). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure to give a brown residue which was purified by rapid chromatography on silica gel using chloroform-methanol (9:1 v/v) as eluant to afford **(99)** in a mixture with triphenylphosphine oxide as a brown oil. This material was mixed with 2M aqueous hydrochloric acid (5 ml) and the mixture was stirred at 80°C for 2h and then allowed to cool and stirred at room temperature for 16h. The mixture was then extracted with dichloromethane (5 x 3 ml) and these extracts were discarded. The aqueous phase was evaporated to dryness under reduced pressure and the resulting brown solid was dissolved in the minimum volume of water and loaded onto a Dowex 50 x 8-100 (H^+) ion-exchange column (2 cm depth x 1.5 cm diameter). The column was eluted with water (20 ml) followed by 2M aqueous ammonium hydroxide solution (30 ml) and the ninhydrin-active fractions which contained the product (TLC : silica; ethanol:n-butanol:dichloromethane:0.880 ammonia, 3:3:3:1; R_f 0.2) were combined and evaporated under reduced pressure to give 8-epicastanospermine **(100)** (113 mg, 60%) as a straw-coloured oil; δ_H (400 MHz, D_2O) 1.76-1.88 (1H, m, 2-H_A), 2.20 (1H, t, J 11 Hz, 5-H_A), 2.33-2.48 (3H, m, 2-H_B, 3-H_A and 8a-H), 3.24 (1H, m, 3-H_B), 3.38 (1H, dd, J 11, 5.2 Hz, 5-H_B), 3.51 (1H, dd, J 9.6, 3.3 Hz, 7-H), 4.03 (1H, ddd, J 11, 9.6, 5.2 Hz, 6-H), 4.43 (1H, dd, J 3.3, 1.3 Hz, 8-H), 4.62 (1H, m, 1-H), δ_C (100 MHz, D_2O), 36.9 (C-2), 54.3 (C-3), 58.6 (C-5), 70.2 (C-6), 70.9 (C-8a), 71.8 (C-8), 75.5 (C-1), 78.4 (C-7).

8-epicastanospermine (113 mg, 0.597 mmol) was dissolved in 2M aqueous hydrochloric acid (3 ml) and the solution was evaporated to dryness under reduced pressure to give a light-brown crystalline solid which was recrystallized from methanol (-20°C) to furnish 8-epicastanospermine hydrochloride **(100a)** (38 mg, 28%, first crop) as a colourless microcrystalline solid, m.p. 243-245°C (dec.), $[\alpha]^{19}{}_D$ + 58.4° (c 0.55 in H_2O) (Found : C, 42.30; H, 7.35; N, 6.07%. $C_8H_{15}NO_4$.HCl requires C, 42.58; H, 7.15; N, 6.20%); υ_{max} (nujol mull) 3390, 3300 (br), 3220 (br); δ_H (D_2O) 2.03 (1H, m), 2.58 (1H, m), 2.94 (1H, t, J 11.5 Hz), 3.17 (1H, m), 3.40 (1H, m), 3.67 (1H, dd, J 9.6, 2.9 Hz), 3.72-3.86 (2H, m), 4.14 (1H, ddd, J 11, 9.5, 5.3 Hz), 4.60 (1H, m), 4.65-4.90 (1H, m (under HOD peak)); m/z (+FAB) 190 (M^+, 100%). (-FAB) 128 (100%), 129 (34), 219 (48), 311 (10).

The Synthesis of Tetrahydroxyindolizidine (106) from Octitol (91)

i) 8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-imino-3,5;6,7-di-*O*-isopropylidene-octitol **(95)**

The diol **(91)** (1.43 g, 3.50 mmol) was converted to the di-*O*-isopropylidene derivative **(101)** using the same procedure employed for the conversion of **(90)** to **(96)** and the product was purified by chromatography on silica gel using petrol-ethyl acetate (4:1 v/v) to give **(101)** (863 mg, 55%) as a colourless oil (Found : MH^+, 450.2491. $C_{24}H_{36}NO_7$ requires 450.2482); υ_{max} (film) 1685 cm^{-1}; δ_H 1.20-1.28 (3H, m, $\underline{CH_3}CH_2$), 1.29-1.36 (6H, 2 x s, $OCMe_A$ and $OCMe_B$), 1.38-1.43 (6H, 2 x s, $OCMe_C$ and $OCMe_D$), 1.71 (1H, m, 2-H_A), 1.86 (1H, dd, J 13, 6 Hz, 2-H_B), 3.37 (1H, td, J 11.4, 5.5 Hz), 3.50-3.99 (5H, m), 4.08 (2H, m, $CH_3\underline{CH_2}$), 4.29 (1H, t, J 5 Hz), 4.36-4.65 (2H, m), 4.59 (1H, d, J 12 Hz, $Ph\underline{CH_A}$), 4.67 (1H, d, J 12 Hz, $Ph\underline{CH_B}$), 7.24-7.40 (5H, Ph); δ_C 14.6 ($\underline{C}H_3CH_2$), 24.0 ($OC\underline{Me_A}$), 24.2 ($OC\underline{Me_B}$), 26.7 ($OC\underline{Me_C}$), 27.7 ($OC\underline{Me_D}$), 31.6 (C-2), 45.6 (C-1), 59.9 (CH), 61.2 (CH_2), 71.2 (CH), 72.4 (CH (br)), 73.3 (CH_2), 75.3 (CH (br)), 78.9 (CH), 99.6 ($O\underline{C}Me_2$), 109.3 ($O\underline{C}Me_2$), 127.5 (Ph_{CH}), 127.7 (Ph_{CH}), 128.2 (Ph_{CH}), 138.3 ($Ph_{Cquaternary}$), 155.3 (O-C=O); m/z (C.I.) 450 (MH^+, 65%), 434 (29), 406 (23), 392 (65), 374 (4), 360 (10), 334 (12), 316 (4), 302 (9), 284 (43), 270 (6), 228 (4), 170 (4), 141 (100).

ii) 1,2,4-Trideoxy-1,4-imino-3,5;6,7-di-*O*-isopropylidene-octitol **(103)**

The di-*O*-isopropylidene derivative **(101)** (850 mg, 1.89 mmol) was converted to the amino alcohol **(103)** using the same procedure employed for the conversion of **(96)** to **(98)**. The crude product was purified by chromatography on silica gel using ethyl acetate-triethylamine (9:1 v/v) as eluant to give **(103)** (329 mg, 62%) as a straw-coloured oil (Found : MH^+ 288.1811. $C_{14}H_{26}NO_5$ requires 288.1811); υ_{max} (film) 3330 (br), 2240 cm^{-1}; δ_H 1.32-1.38 (6H, 2 x s, OC$\underline{Me}_A$ and OC$\underline{Me}_B$), 1.40-1.46 (6H, 2 x s, OC$\underline{Me}_C$ and OC$\underline{Me}_D$), 1.85 (1H, m, 2-H_A), 1.96-2.12 (1H, m, 2-H_B), 2.82-2.93 (1H, m), 3.24 (1H, dt, J 10, 7 Hz), 3.30 (1H, dd, J 9, 5.7 Hz), 3.55 (1H, t, J 8 Hz), 3.74 (2H, d, J 5 Hz), 3.86 (1H, t, J 7.5 Hz), 4.01 (1H, dt, J 8, 5 Hz), 4.33 (1H, m); δ_C 23.6 (OC$\underline{Me}_A$), 24.7 (OC$\underline{Me}_B$), 26.8 (OC$\underline{Me}_C$), 26.9 (OC$\underline{Me}_D$), 32.6 (C-2), 44.9 (C-1), 62.5 (CH), 62.9 (C-8), 71.3 (CH), 72.4 (CH), 79.6 (CH), 80.3 (CH), 99.9 (O$\underline{C}Me_2$), 109.3 (O$\underline{C}Me_2$); m/z (C.I.) 288 (MH^+, 45%), 272 (5), 230 (15), 211 (3), 196 (2), 172 (2), 155 (4), 125 (4), 97 (9), 69 (100).

(iii) 1,8;6,7-di-*O*-isopropylidene-1,6,7,8-tetrahydroxyindolizidine **(104)**

To a solution of **(103)** (126 mg, 0.44 mmol) in THF (3 ml) were added sequentially diisopropylethylamine (114 mg, 0.154 ml, 0.88 mmol), triphenylphosphine (230 mg, 0.88 mmol) and carbon tetrabromide (292 mg, 0.88 mmol) and the mixture was stirred vigorously at room temperature for 16h. After this time, the mixture was poured onto saturated aqueous sodium hydrogen carbonate solution (15 ml) and extracted with dichloromethane (4 x 7 ml). The combined extracts were dried (K_2CO_3) and evporated under reduced pressure. The residue was chromatographed on silica gel using chloroform-methanol (9:1 v/v) as eluant to give initially triphenylphosphine oxide, followed by **(104)** (94 mg, 79%) as a tan oil (Found : MH^+ 270.1735. $C_{14}H_{24}NO_4$ requires 270.1705); δ_H 1.33 (3H, s, $OCMe_A$), 1.36 (3H, s, $OCMe_B$), 1.44 (3H, s, $OCMe_C$), 1.47 (3H, s, $OCMe_D$), 1.82 (1H, m, 2-H_A), 2.02 (1H, sextet, J 6.8 Hz, 2-H_B), 2.84 (1H, m, 3-H_A), 3.12 (1H, dt, J 10, 6.8 Hz, 3-H_B), 3.27 (1H, dd, J 8.7, 5.7 Hz, 8a-H), 3.47 (1H, dd, J 10.8, 6 Hz, 5-H_A), 3.53 (1H, dd, J 8.7, 7.2 Hz, 8-H), 3.63 (1H, dd, J 10.8, 3.6 Hz, 5-H_B), 3,88 (1H, t, J 7.2 Hz, 7-H), 4.20 (1H, ddd, J 7.2, 6, 3.6 Hz, 6-H), 4.32 (1H, m, 1-H); δ_C 23.7 ($OC\underline{Me}_A$), 24.9 ($OC\underline{Me}_B$), 27.2 ($OC\underline{Me}_C$ and $OC\underline{Me}_{1D}$), 32.8 (C-2), 33.5 (C-5), 45.1 (C-3), 62.8 (CH), 71.5 (CH), 72.9 (CH), 79.4 (CH), 80.9 (CH), 99.9 ($O\underline{C}Me_2$), 110.2 ($O\underline{C}Me_2$); m/z (C.I.) 270 (MH^+, 19%), 212 (10), 201 (1), 154 (3), 128 (5), 82 (5), 69 (100).

iv) **Tetrahydroxyindolizidine (105)**

Indolizidine **(104)** (86 mg, 0.318 mmol) was dissolved in 2M aqueous hydrochloric acid (4 ml) and the mixture was stirred at 80°C for 3 h and then allowed to cool and stirred at room temperature for 16h. The mixture was evaporated to dryness under reduced pressure and the residue was purified by ion-exchange chromatography as described for the preparation of 8-epicastanospermine. The product was obtained as an oil which crystallized on standing. Recrystallization from ethanol provided tetrahydroxyindolizidine **(105)** (11 mg, 18%, 1st crop) as colourless needles, m.p. 168-169.5°C (dec.), $[\alpha]^{22}_D$ -30.3° (c 0.15 in H_2O) (Found : MH^+, 190.1080. $C_8H_{16}NO_4$ requires 190.1079); υ_{max} (nujol mull) 3340 (br), 3230 cm^{-1}; δ_H (D_2O) 1.82 (1H, m), 2.00 (1H, m), 2.87 (1H, m), 2.97-3.10 (2H, m), 3.81-3.89 (2H, m), 3.93 (1H, dd, J 10, 3.5 Hz), 4.14-4.20 (2H, m), 4.39 (1H, m); m/z (C.I.) 190 (MH^+, 41%), 172 (4), 130 (4), 86 (100).

Reduction of mixed fractions --

8-*O*-Benzyl-1,2,4-trideoxy-*N*-ethoxycarbonyl-1,4-*O*-isopropylidene-octitol **(108)**

To a solution of mixed fractions (from large scale preparation of octuloses **(87)**) (2.20 g, 5.4 mmol) in THF (60 ml) at -78°C was added diisobutylaluminium hydride (1.5M in toluene, 9.0 ml, 13.50 mmol) dropwise. The reaction mixture was stirred at -78°C for 1h and then saturated aqueous ammonium chloride solution (25 ml) was added dropwise. The mixture was allowed to warm to room temperature over 30-40 min, poured onto 2M aqueous hydrochloric acid (150 ml) and extracted with ethyl acetate (4 x 50 ml). The combined extracts were dried ($MgSO_4$) and evporated under reduced pressure and purification of the residue by chromatography on silica gel using petrol-ethyl acetate (40:60 v/v) as eluant afforded a colourless oil (1.0 g, 45%) homogeneous by TLC (silica; ethyl acetate ; R_f 0.65) followed by a minor product which was not examined further. The colourless oil (1.0 g) was converted to di-*O*-isopropylidene derivatives **(108)** and **(96)** by the same procedure employed for the conversion of **(90)** to **(96)**. The products were separated by chromatography on silica gel using petrol-ethyl acetate (3:1 - 5:2 v/v) as eluant, giving first eluted **(108)** (388 mg, 16% from mixed fractions) as a colourless oil (Found : MH^+, 450.2491. $C_{24}H_{36}NO_7$ requires 450.2492); υ_{max} (film) 1685 cm^{-1}; δ_H 1.16-1.30 (6H, m, $C\underline{H}_3CH_2$ and $OCMe_A$), 1.36 (3H, s, $OCMe_B$), 1.43 (3H, s, $OCMe_C$), 1.45 (3H, s, $OCMe_D$), 1.71-1.95 (2H, m, 2-H_2), 3.25-3.46 (2H, m,(br)), 3.52 (1H, d, J 10, 4.5 Hz), 3.56-3.69 (1H, m,(br)), 3.71-4.48 (7H, m), 4.54 (1H, d, J 12.2 Hz, $PhC\underline{H}_A$), 4.61 (1H, d, J 12.2Hz, $PhC\underline{H}_B$), 7.20-7.41 (5H, m, Ph); m/z (C.I.) 450 (MH^+, 7%), 434 (4), 392 (7), 284 (4), 270 (4), 170 (4), 141 (100).

Further elution afforded **(96)** (370 mg, 15.7% from mixed fractions).

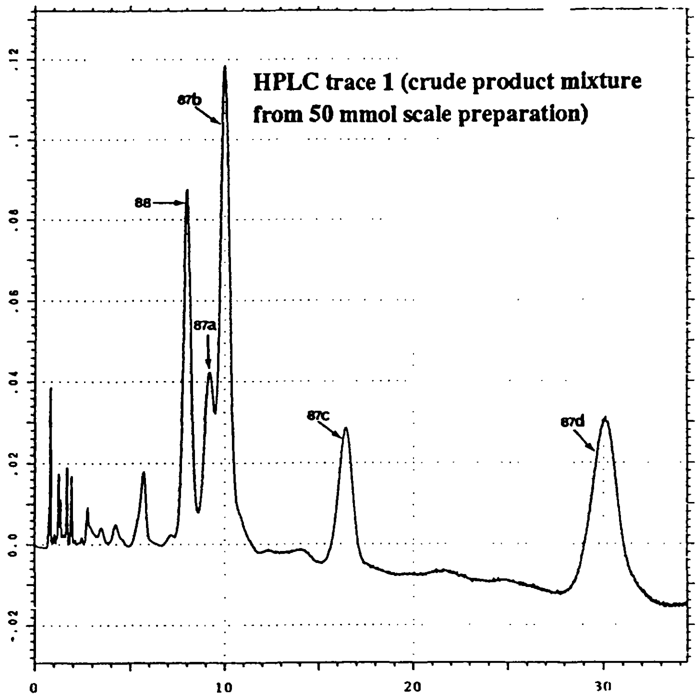
1,2,4-Trideoxy-1,4-imino-3,5;6,7-di-*O*-isopropylideneoctitol **(109)**

The di-*O*-isopropylidene derivative **(108)** (374 mg, 0.833 mmol) was converted to the amino alcohol **(109)** by the same procedure employed for the conversion of **(96)** to **(98)**. The crude product was purified by chromatography on silica gel using chloroform-methanol (9:1 v/v) as eluant to give **(109)** as a straw-coloured oil (Found : MH^+, 288.1811. $C_{14}H_{26}NO_5$ requires 288.1811); υ_{max} (film) 3330 (br) cm^{-1}; δ_H 1.35 (3H, s, $OCMe_A$), 1.39 (3H, s, $OCMe_B$), 1.42 (3H, s, $OCMe_C$), 1.44 (3H, s, $OCMe_D$), 1.92-2.02 (2H, m, 2-H_2), 3.02-3.25 (2H, m), 3.22-3.45 (2H, m(br), NH and OH), 3.60-3.85 (4H, m), 4.12-4.23 (2H, m), 4.37-4.45 (1H, m(br)); m/z (C.I.) 288 (MH^+, 100%), 272 (23), 230 (71), 214 (7), 172 (10), 155 (18).

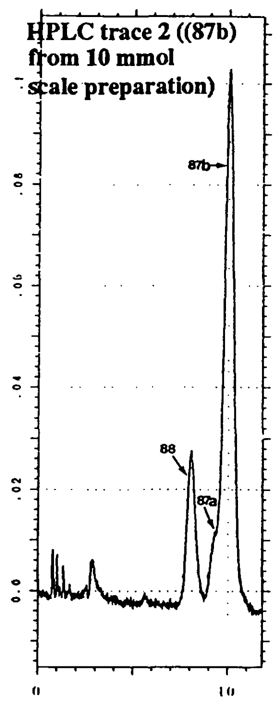
APPENDICES

APPENDIX 1

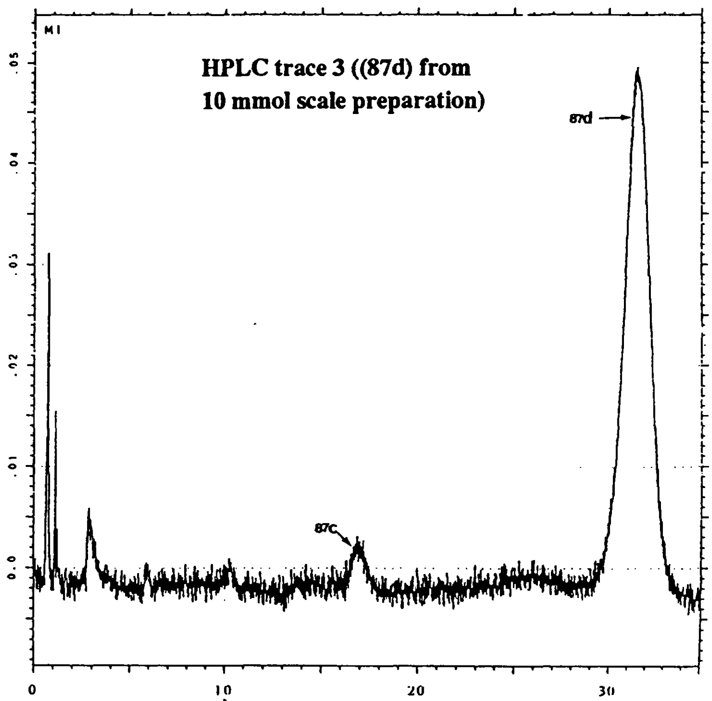
HPLC analysis/separation of diastereoisomers **(87a/b/c/d).**



HPLC trace 1 (crude product mixture from 50 mmol scale preparation)



HPLC trace 2 ((87b) from 10 mmol scale preparation)



HPLC trace 3 ((87d) from 10 mmol scale preparation)

Analytical HPLC traces 1-3 were obtained using the following conditions:-

CONDITIONS 1

COLUMN: Lichrosorb Diol (10μm), 250 x 4.6 mm, ID # 383X

ELUANT: Hexane - isopropyl alcohol (99.5 : 0.5 v/v)

FLOW RATE: 4.0 ml min^{-1}

DETECTION: UV at 210 nm

Semi-preparative separation of **(87c)** and **(87d)** from the mixed fractions (from medium scale aldol/deethoxycarbonylation, 40 mg, in six injections) was achieved using the following conditions:-

CONDITIONS 2

COLUMN: Lichrosorb Diol (10μm), 250 x 10 mm, ID # 17X

ELUANT: Hexane - isopropyl alcohol (99:1 v/v)

FLOW RATE: 8 ml min^{-1}

DETECTION: UV at 220 nm

This separation afforded **(87c)** (9.5 mg, approximately 90% pure), **(87d)** (6.8 mg, >96% pure) and a mixture of **(88)/(87a)/(87b)** (yield not measured) (The identity and purity of these samples were checked by analytical HPLC using Conditions 4 below)

Semi-preparative separation of **(88)**, **(87b)** and a 70:30 mixture of **(87a)**:**(87c)** from the mixture of **(88)**/**(87a)**/**(87b)** was achieved using the following conditions:-

CONDITIONS 3

COLUMN: Rainin Microsorb silica (5μm), 250 x 4.6 mm, ID # 424S
ELUANT: Hexane - isopropyl alcohol (98:2 v/v)
FLOW RATE: 4 ml min^{-1}
DETECTION: UV at 220 nm

This separation afforded **(88)** (0.6 mg), **(87b)** (3.5 mg, approximately 95% pure) and a 70:30 mixture of **(87a)**:**(87c)** (2.8 mg). (The identity and purity of these samples were checked by analytical HPLC using both conditions 1 (above) and conditions 4 (below) except that in both cases the UV detection wavelength used was 220 nm.)

The final semi-preparative separation of **(87a)** (+ approximately 10% **(87c)**) from the 70:30 mixture of **(87a)**:**(87c)** was achieved using the following conditions:-

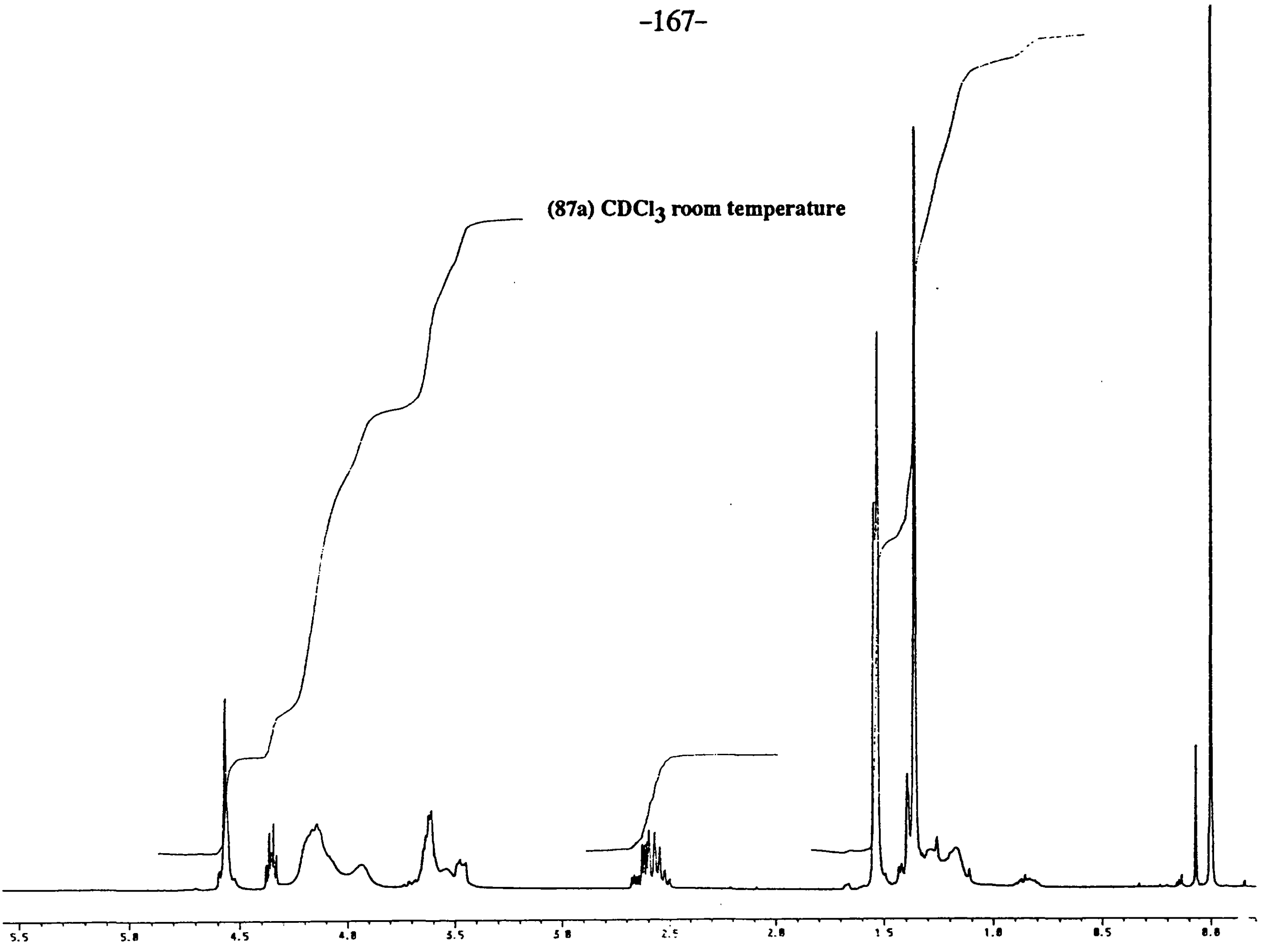
CONDITIONS 4

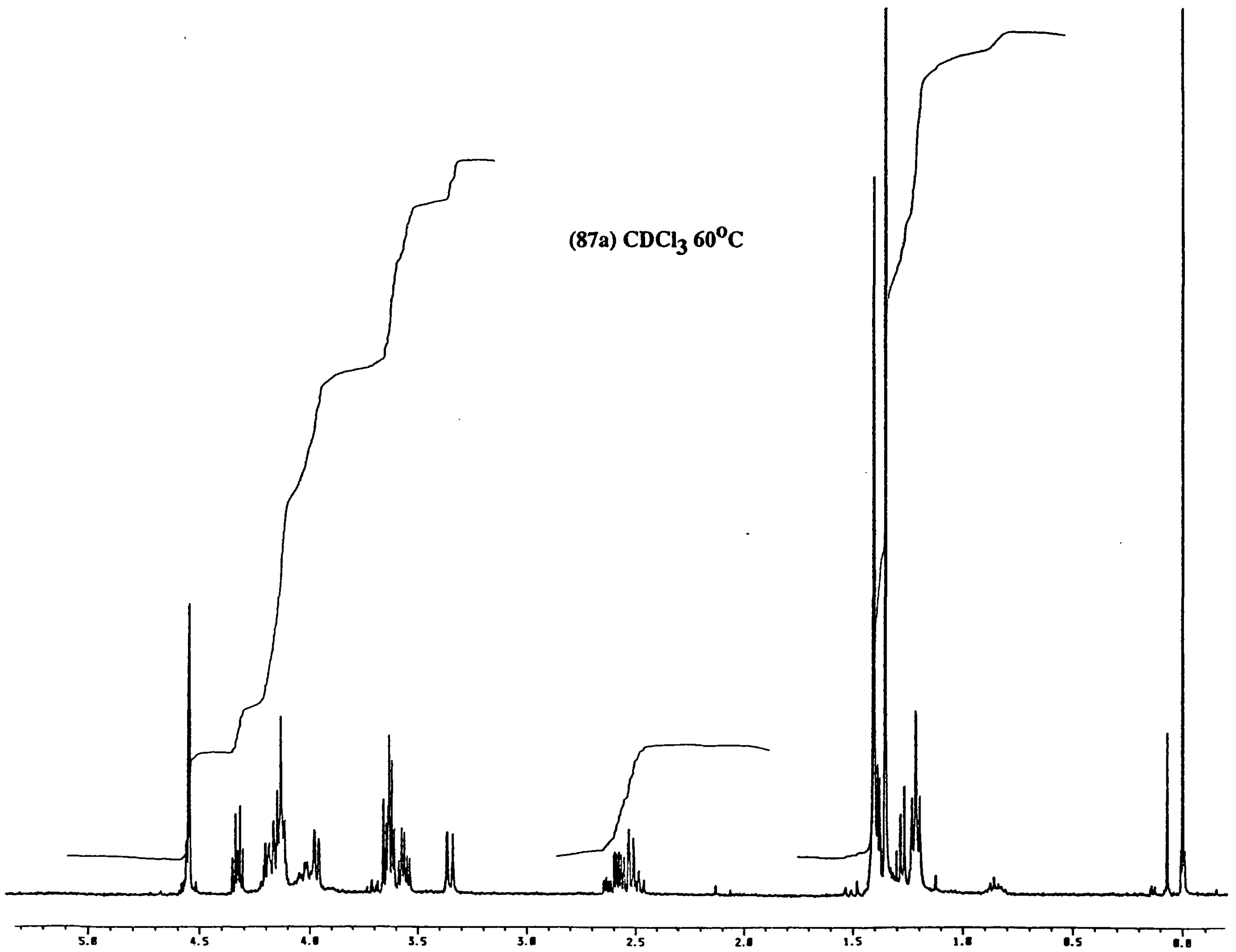
COLUMN: Lichrosorb Diol (10μm), 250 x 4.6 mm, ID # 383X
ELUANT: Hexane - isopropyl alcohol (99:1 v/v)
FLOW RATE: 3 ml min^{-1}
DETECTION: UV at 220 nm

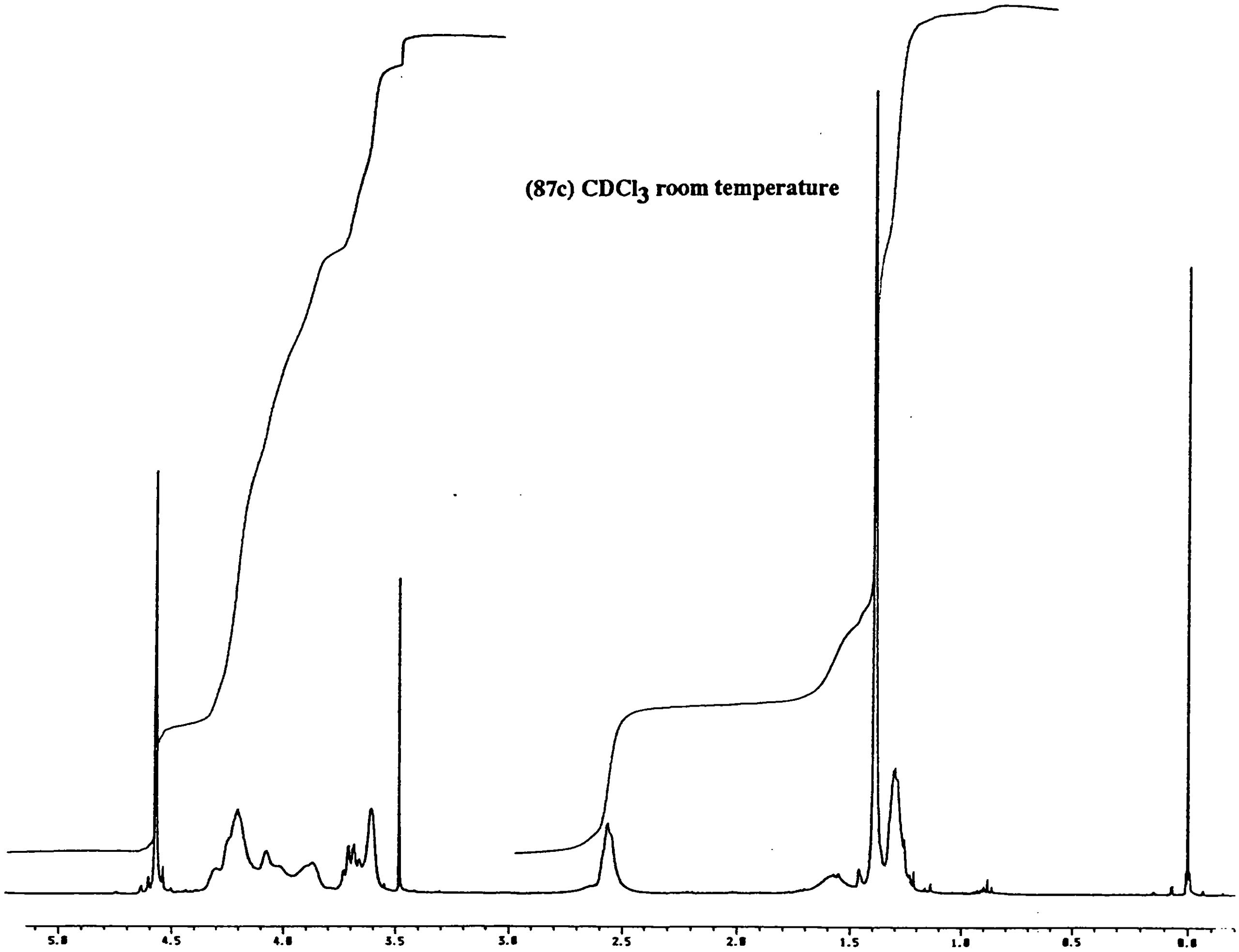
This separation afforded **(87a)** (+ approximately 10% **(87c)**) (1.75 mg) (Purity checked by analytical HPLC using conditions 1 above except that the UV detection wavelength used was 220 nm.)

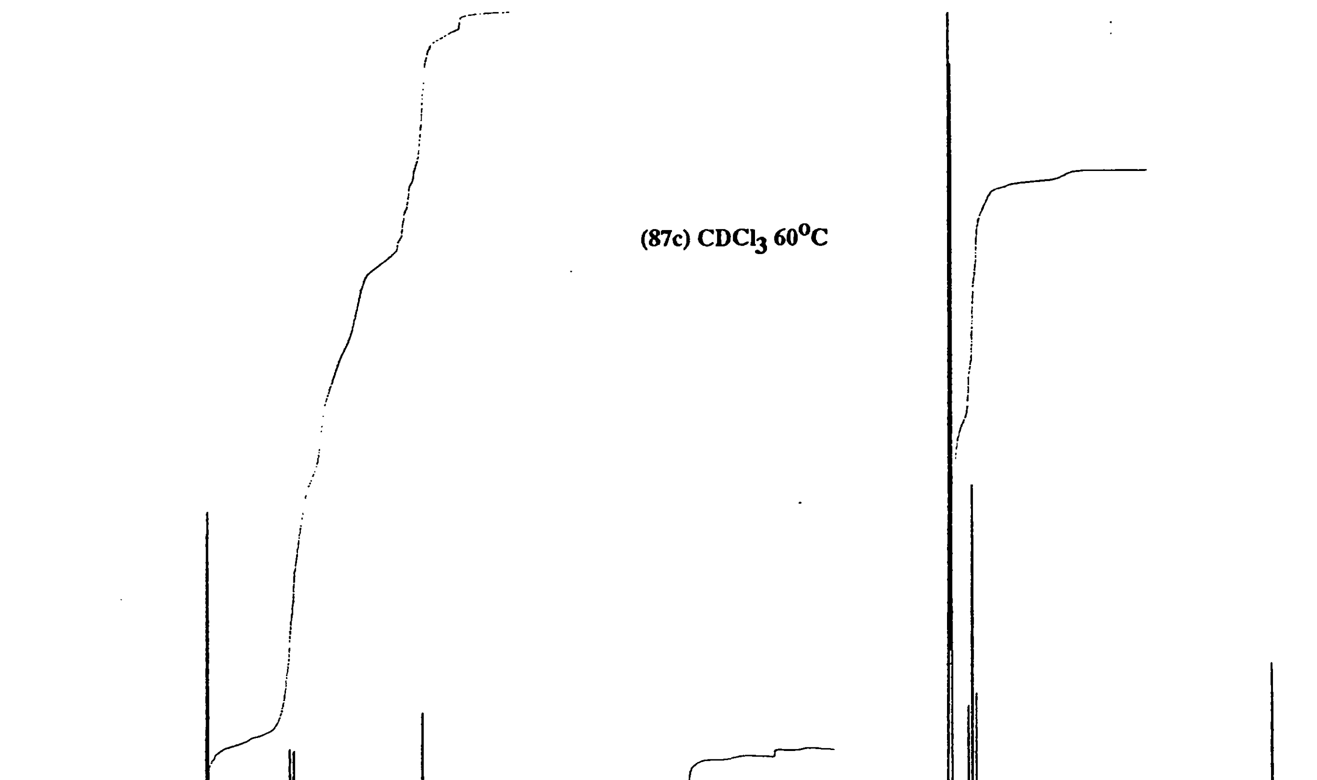
APPENDIX 2

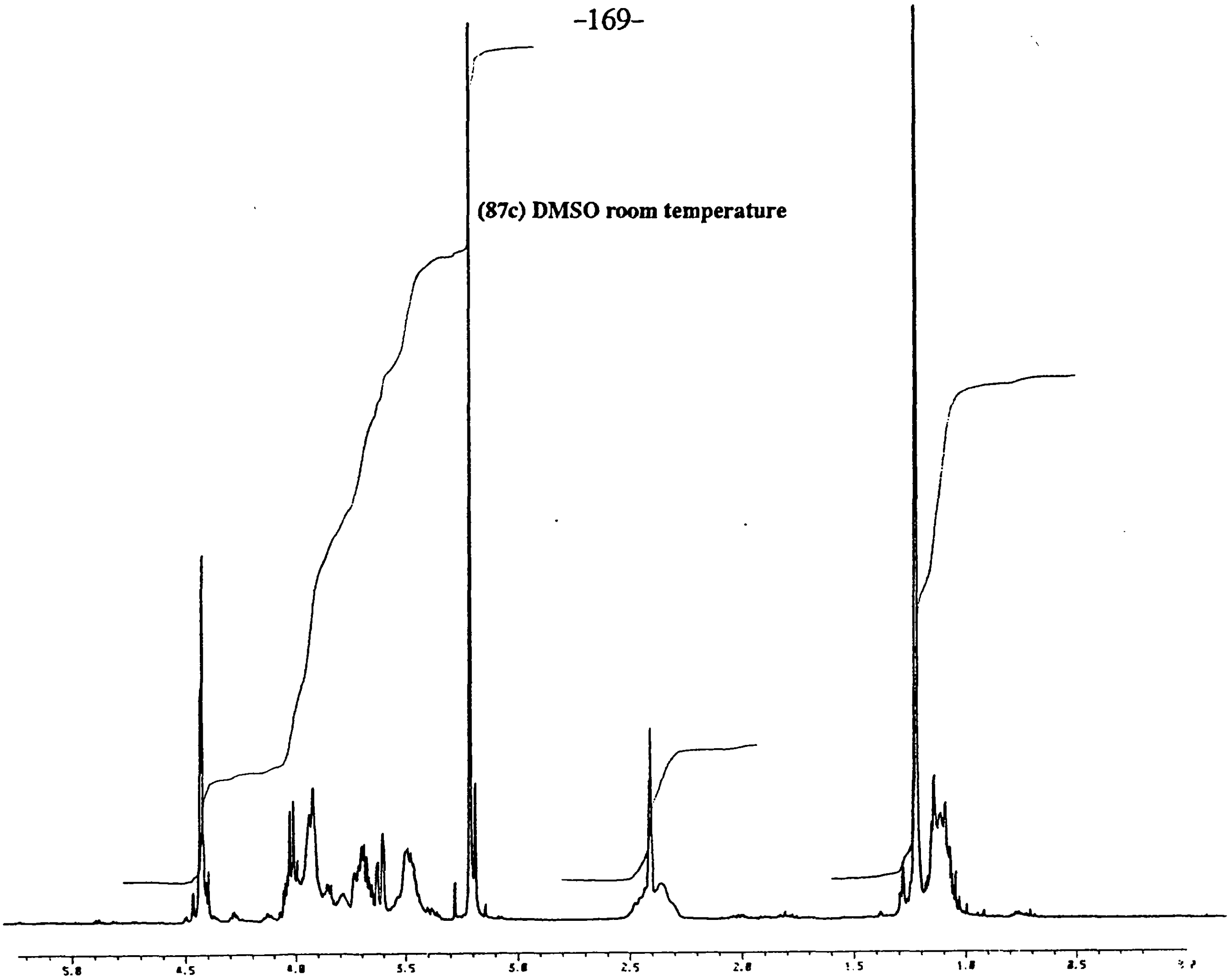
400 MHz ^{1}H nmr spectra of minor diastereoisomers **(87a)** and **(87c)** at room temperature and at 60°C ($CDCl_3$) and 80°C ((**87c**),DMSO).

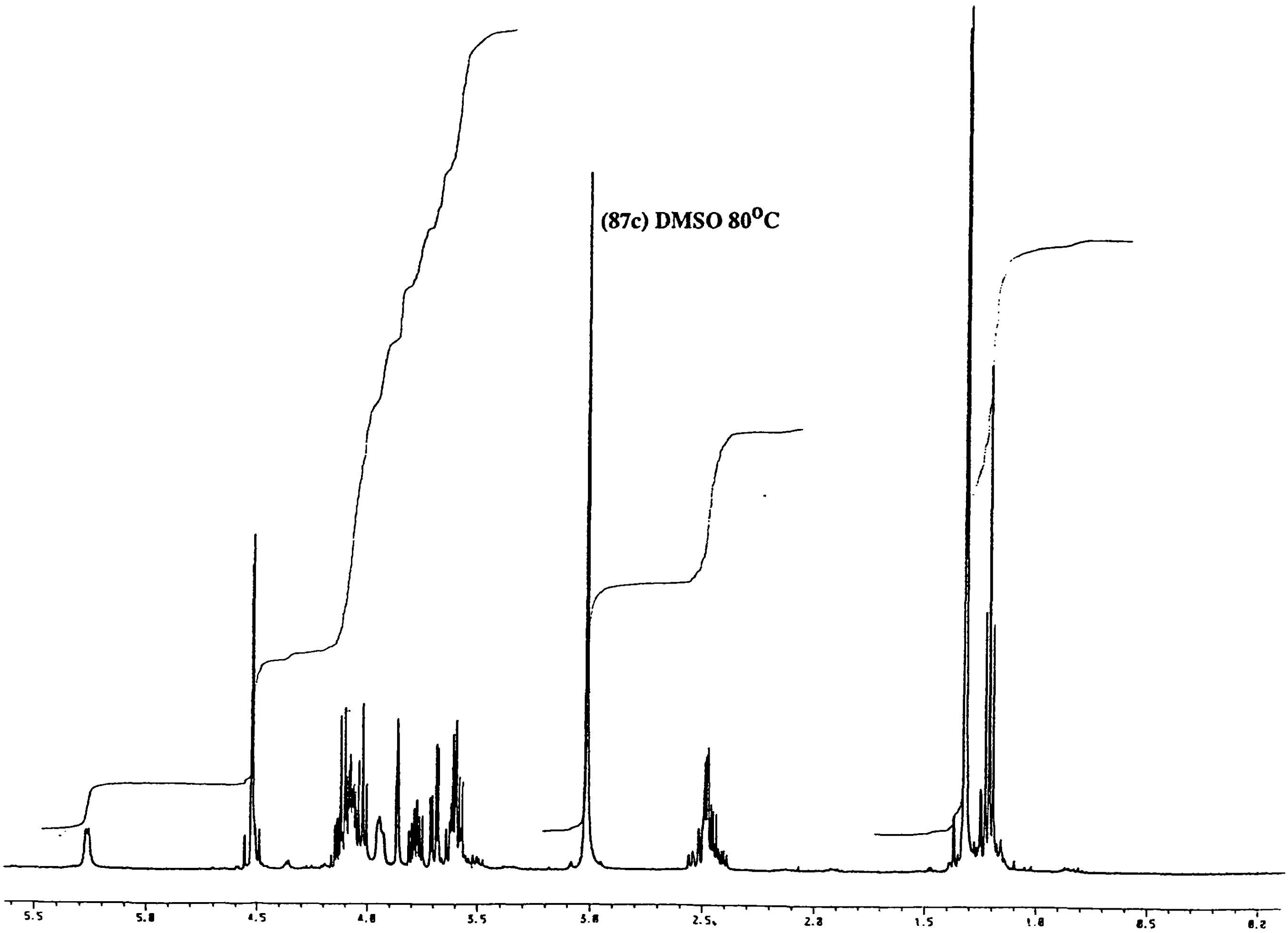

(87a) $CDCl_3$ room temperature


(87a) $CDCl_3$ 60°C


(87c) $CDCl_3$ room temperature
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


(87c) $CDCl_3$ 60°C
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


(87c) DMSO room temperature


(87c) DMSO 80^{0}C

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PUBLICATIONS

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